Exhibit E

LEXSEE 52 FED. REG. 17830

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

AGENCY: Food and Drug Administration.

[FDA 225-86-8251]

52 FR 17830

May 12, 1987

Memorandum of Understanding Between the Patent and Trademark Office and the Food and Drug Administration
ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing notice of a memorandum of understanding (MOU) between the Patent and Trademark Office (PTO) and FDA. The MOU establishes procedures whereby FDA assists PTO in determining a product's eligibility for patent term restoration and procedures for exchanging information between FDA and PTO regarding regulatory review period determinations, due diligence petitions, and informal FDA hearings.

DATE: The memorandum of understanding became effective September 17, 1986.

FOR FURTHER INFORMATION CONTACT:Walter J. Kustka, Intergovernmental and Industry Affairs Staff (HFC-50), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1583.

TEXT: SUPPLEMENTARY INFORMATION: In accordance with *21 CFR 20.108(c)*, which states that all agreements and memorandum of understanding between FDA and others shall be published in the Federal Register, the agency is publishing this memorandum of understanding.

Dated: May 5, 1987.

John M. Taylor,

Associate Commissioner for Regulatory Affairs.

Memorandum of Understanding Between the Patent and Trademark Office and the Food and Drug Administration

I. Purpose

This agreement establishes the procedures whereby the Food and Drug Administration (FDA) assists the Patent and Trademark Office (PTO) in determining a product's eligibility for patent term restoration under *35 U.S.C. 156.* It also establishes procedures for exchanging information between FDA and PTO regarding regulatory review period determinations, due diligence petitions and informal FDA hearings under the law.

II. Background

The patent term restoration portion of the Drug Price Competition and Patent Term Restoration Act of 1987 (Pub. L. 98-417) was designed to create new incentives for research and development of certain products which are subject to premarket government approval. These provisions enable the owners of patents on certain human drugs, medical de-

vices, and food or color additives to attempt to restore to the terms of those patents some of the patent time lost while awaiting premarket government approval.

Under the patent term restoration sections of the Act, a patent which claims a human drug product, medical device, food or color additive first approved for marketing after September 24, 1984 may qualify for patent term extension. Regardless of whether the patent claims a product, a method of using a product, or a method of manufacturing a product, the applicant for a patent term extension must establish that:

(1) The patent has not expired *(35 U.S.C. 156*(a)(1)),

(2) The patent has never been extended *(35 U.S.C. 156*(a)(2)),

(3) The applicant for extension is submitted by the owner of record of the patent or its agent and includes details relating to the patent and regulatory review time spent in securing FDA approval *(35 U.S.C. 156*(a)(3)),

(4) The product has been subject to a regulatory review period within the meaning of *35 U.S.C. 156*(g) before its commercial marketing or use *(35 U.S.C. 156*(a)(4)),

(5) The approval:

(A) Is the first permitted commerical marketing or use of the product, or

(B) In the case of products manufactured using recombinant DNA technology, it is the first permitted commercial marketing or use of a product manufactured under the process claimed in the patent *(35 U.S.C. 156*(a)(5)), and

(6) The application for extension of the term of the patent was submitted to PTO within 60 days of FDA approval of the commercial marketing application *(35 U.S.C. 156*(d)(1)).

While it is the responsibility of the Commissioner of Patents and Trademarks to decide whether an applicant has satisfied these six conditions, FDA possesses expertise and records regarding the last four and has certain direct responsibilities under *35 U.S.C. 156* for determining the length of the regulatory review period. Consequently, to facilitate eligiblity decisions and permit FDA and PTO to carry out their responsibilities under *35 U.S.C. 156*, the FDA and PTO have entered into this agreement. This agreement is consistent with the authority contained in section 702(d) of the Federal Food, Drug, and Cosmetic Act.

Under this agreement, FDA, upon receipt of a written request from PTO, will convey to PTO the following information regarding eligibility for extension: (1) Whether a product has undergone a regulatory review period within the meaning of *35 U.S.C. 156*(g) prior to commercialization, (2) whether the marketing permission was for the first permitted commercial marketing or use of that product, or, in the case of recombinant marketing or use of that product, or, in the case of recombinant DNA technology, whether such commercial marketing or use was the first permitted under the process claimed in the patent, and (3) whether the patent term extension application, as well as any other relevant information. Similarly, upon a request by PTO and the receipt of a copy of the application for patent term extension, FDA will determine the application for patent term extension, FDA will determine the length of the regulatory review period for the approved product.

The procedures covered by this agreement extend from the date of PTO's request for information on eligibility to the resolution of due diligence petitions and information hearings. The regulatory review period determination is not final until due diligence petitions and informal hearings, if any, have been resolved. A certificate for extension of the term of a patent may not issue from PTO until the regulatory review period determination is final unless an interim extension appears warranted under *35 U.S.C. 156*(e)(2).

III. Substance of the Agreement: Patent Term Extension Applications Under *35 U.S.C. 156*

A. Eligibility Determination Assistance:

1. Upon deciding that a patent term extension application is complete and meets basic formal requirements, the PTO will send a written request to FDA requesting that FDA:

a. verify whether the product:

(1) Was subject to a regulatory review period within the meaning of *35 U.S.C. 156*(g) prior to its commercial marketing or use, and

(2) Represents either the first permitted commercial marketing or use of that product, or, in the case of recombinant DNA technology, the first permitted commercial marketing or use of the product manufactured under the process claimed in the patent.

b. Inform PTO whether the patent term restoration application was submitted within 60 days after the product was approved.

2. Additionally, PTO, in its written request, shall clearly state that it is not requesting determination of the product's regulatory review period at this time.

3. FDA will consult its records and experts and, through the Director of the Health Assessment Policy Staff, Office of Health Affairs, issue a written response to the Director of Patent Examining Group 120, PTO, on each of these questions.

4. FDA, consistent with the authority contained in section 702(d) of the Federal Food, Drug, and Cosmetic Act with respect to drugs, will provide PTO with any other information relevant to the product's eligibility.

5. FDA, upon written request, will also provide assistance to PTO in petitions before the Commissioner of Patents and Trademarks regarding eligibility determinations.

B. Regulatory Review Period Determinations:

1. Should the PTO decide that the product is eligible for patent term restoration, it will send FDA a copy of the application for patent term restoration and a written request to determine the length of the product's regulatory review period. The copy and request will be sent to FDA within 60 days of the application's receipt by PTO.

2. FDA will consult its records, determine the entire length of the regulatory review period, and, through the Associate Commissioner for Health Affairs, issue a written statement of that determination to the Commissioner of Patents and Trademarks. The determination will be made within 30 days after the receipt of the application and written request from PTO. Additionally, FDA will publish its determination in the Federal Register.

C. Due Diligence Petitions and Hearing Requests:

1. Due diligence petitions must be filed at FDA within 180 days of the publication of a product's regulatory review period in the Federal Register.

a. If no due diligence petition is received by FDA within the 180-day filing period, FDA will promptly notify PTO in writing that the regulatory review period determination is final.

b. If a due diligence petition which satisfies statutory and regulatory requirements is received by FDA,

(1) FDA will promptly notify PTO in writing of the receipt of the petition,

(2) PTO will refrain from issuing a certificate of extension pending a final determination of the regulatory review period unless an interim extension appears warranted under *35 U.S.C. 156*(e)(2),

(3) FDA will determine whether the applicant acted with due diligence within 90 days after receipt of such a petition and will send written notification to the Commissioner of Patents and Trademarks as to any modification in the length of the regulatory review period, and

(4) FDA will also publish its due diligence determination, together with the full factual and legal bases for FDA's decision, in the Federal Register.

2. Requests for an informal hearing on FDA's due diligence determination must be received by FDA within 60 days of the publication of the due diligence determination in the Federal Register.

a. If FDA does not receive any request for an informal hearing within the 60 filing period, FDA will notify PTO in writing that the regulatory review period determination, as modified, if at all, by the due diligence determination, is final.

b. If FDA receives a request for an informal hearing within the 60 day filing period,

(1) FDA will notify PTO in writing of the hearing request,

(2) PTO will refrain from issuing a certificate of extension pending final determination of the regulatory review period unless an interim extension appears warranted under *35 U.S.C. 156*(e)(2), and

(3) FDA will affirm or revise the determination that was the subject of the hearing within 30 days after completion of the hearing and will notify the Commissioner of Patents and Trademarks in writing of its decision and whether the determination of the regulatory review period is now final. Additionally, FDA will publish its findings in the Federal Register.

D. Supplemental Information:

Should either agency receive information which is relevant to the patent term restoration of a patent during any stage of these eligibility or regulatory review period determinations, that agency will promptly notify the other and provide documentation as available.

E. Availabilty of Information:

Copies of all letters required by this agreement and exchanged between PTO and FDA will be placed in the file for each product subject to patent term restoration. These files are available for review at FDA's Dockets Management Branch (HFA-305), Room 4-62 5600 Fishers Lane, Rockville, Maryland 20857 and at the Patent and Trademark Office, Crystal Plaza Building 2-9A09, 2011 Jefferson Davis Highway, Arlington, Virginia 22202.

IV Names and Addresses of Participating Parties

A. Patent and Trademark Office, Washington, DC 20231.

B. Food and Drug Administration, 5600 Fishers Lane, Rockville Maryland 20857.

V. Liaison Officers

A. *Liaison Officer for the Patent and Trademark Office:* Director, Patent Examining Group 120, (currently Charles E. Van Horn, Esq.), Patent and Trademark Office, Washington, DC 20231, (703-557-3637).

B. *Liaison Officer for the Food and Drug Administration:* Director, Health Assessment Policy Staff (HFY-20), (currently Ronald L. Wilson), Office of Health Affairs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857, (301-443-1382).

VI. Period of Agreement

This agreement, when accepted by both parties, will be effective indefinitely. It may be modified by mutual written consent or terminated by either party upon a thirty day advance written notice to the other party.

APPROVED AND ACCEPTED FOR THE PATENT AND TRADEMARK OFFICE.

By: Donald J. Quigg,

Title: Assistant Secretary and Commissioner of Patents and Trademarks.

Dated: September 17, 1986.

APPROVED AND ACCEPTED FOR FOOD AND DRUG ADMINISTRATION.

By: John M. Taylor,

Title: Acting Associate Commissioner for Regulatory Affairs.

Dated: September 3, 1986.

[FR Doc. 87-10713 Filed 5-11-87; 8:45 am]

BILLING CODE 4160-01-M

Exhibit F

Search results from the "OB_Rx" table for query on "019735."

Active Ingredient:	OFLOXACIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	FLOXIN
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	200MG
Application Number:	019735
Product Number:	001
Approval Date:	Dec 28, 1990
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	OFLOXACIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	FLOXIN
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	300MG
Application Number:	019735
Product Number:	002
Approval Date:	Dec 28, 1990
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Active Ingredient:	OFLOXACIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	FLOXIN
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	400MG
Application Number:	019735
Product Number:	003
Approval Date:	Dec 28, 1990
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	**AB**
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through September, 2008

Patent and Generic Drug Product Data Last Updated: October 20, 2008

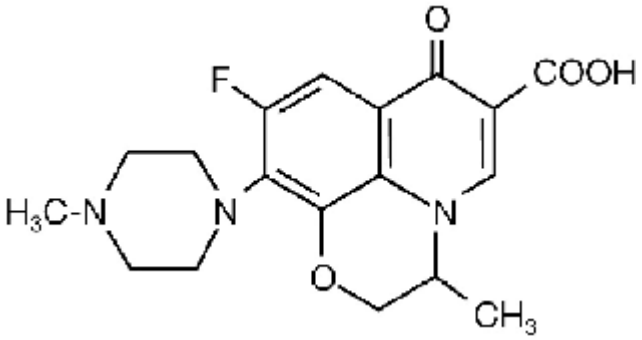
FLOXIN® Tablets
(Ofloxacin Tablets)

WARNING:
Fluoroquinolones, including FLOXIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLOXIN® (ofloxacin tablets) Tablets and other antibacterial drugs, FLOXIN® (ofloxacin tablets) Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

FLOXIN® (ofloxacin tablets) Tablets is a synthetic broad-spectrum antimicrobial agent for oral administration. Chemically, ofloxacin, a fluorinated carboxyquinolone, is the racemate, (±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid. The chemical structure is:



Its empirical formula is $C_{18}H_{20}FN_3O_4$, and its molecular weight is 361.4 Ofloxacin is an off-white to pale yellow crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine. The relative solubility characteristics of ofloxacin at room temperature, as defined by USP nomenclature, indicate that ofloxacin is considered to be *soluble* in aqueous solutions with pH between 2 and 5. It is *sparingly* to *slightly soluble* in aqueous solutions with pH 7 (solubility falls to 4 mg/mL) and *freely soluble* in aqueous solutions with pH above 9. Ofloxacin has the potential to form stable coordination compounds with many metal ions. This *in vitro* chelation potential has the following formation order: $Fe^{+3} > Al^{+3} > Cu^{+2} > Ni^{+2} > Pb^{+2} > Zn^{+2} > Mg^{+2} > Ca^{+2} > Ba^{+2}$.

FLOXIN® Tablets contain the following inactive ingredients: anhydrous lactose, modified corn starch, hydroxypropyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and may also contain synthetic yellow iron oxide.

CLINICAL PHARMACOLOGY

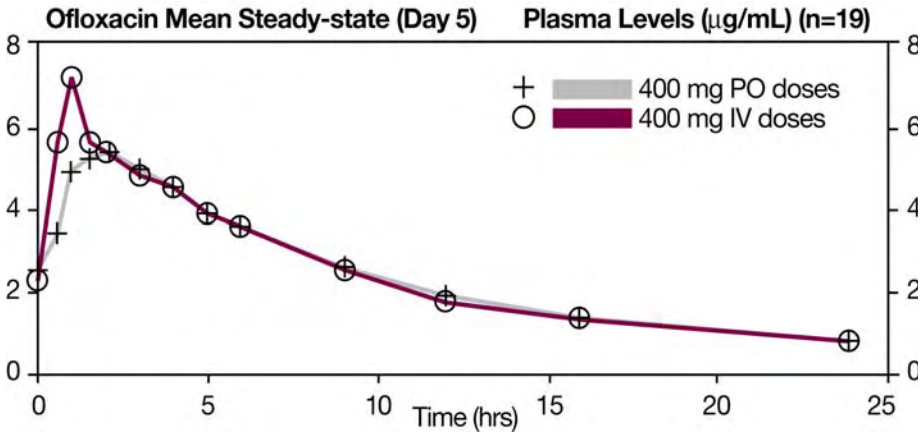
Following oral administration, the bioavailability of ofloxacin in the tablet formulation is approximately 98%. Maximum serum concentrations are achieved one to two hours after an oral dose. Absorption of ofloxacin after single or multiple doses of 200 to 400 mg is predictable, and the amount of drug absorbed increases proportionately with the dose. Ofloxacin has biphasic elimination. Following multiple oral doses at steady-state administration, the half-lives are approximately 4-5 hours and 20-25 hours. However, the longer half-life represents less than 5% of the total AUC. Accumulation at steady-state can be estimated using a half-life of 9 hours. The total clearance and volume of distribution are approximately similar after single or multiple doses. Elimination is mainly by renal excretion. The following are mean peak serum concentrations in healthy 70-80 kg male volunteers after single oral doses of 200, 300, or 400 mg of ofloxacin or after multiple oral doses of 400 mg.

Oral Dose	**Serum Concentration 2 Hours After Admin. (µg/mL)**	**Area Under the Curve ($AUC_{(0-\infty)}$) (µg•h/mL)**
200 mg single dose	1.5	14.1
300 mg single dose	2.4	21.2
400 mg single dose	2.9	31.4
400 mg steady-state	4.6	61.0

Steady-state concentrations were attained after four oral doses, and the area under the curve (AUC) was approximately 40% higher than the AUC after single doses. Therefore, after multiple-dose administration of 200 mg and 300 mg doses, peak serum levels of 2.2 µg/mL and 3.6 µg/mL, respectively, are predicted at steady-state.

In vitro, approximately 32% of the drug in plasma is protein bound.

The single dose and steady-state plasma profiles of ofloxacin injection were comparable in extent of exposure (AUC) to those of ofloxacin tablets when the injectable and tablet formulations of ofloxacin were administered in equal doses (mg/mg) to the same group of subjects. The mean steady-state $AUC_{(0-12)}$ attained after the intravenous administration of 400 mg over 60 min was 43.5 µg•h/mL; the mean steady-state $AUC_{(0-12)}$ attained after the oral administration of 400 mg was 41.2 µg•h/mL (two one-sided t-test, 90% confidence interval was 103-109). (See following chart.)



Between 0 and 6 h following the administration of a single 200 mg oral dose of ofloxacin to 12 healthy volunteers, the average urine ofloxacin concentration was approximately 220 µg/mL. Between 12 and 24 hours after administration, the average urine ofloxacin level was approximately 34 µg/mL.

Following oral administration of recommended therapeutic doses, ofloxacin has been detected in blister fluid, cervix, lung tissue, ovary, prostatic fluid, prostatic tissue, skin, and sputum. The mean concentration of ofloxacin in each of these various body fluids and tissues after one or more doses was 0.8 to 1.5 times the concurrent plasma level. Inadequate data are presently available on the distribution or levels of ofloxacin in the cerebrospinal fluid or brain tissue.

Ofloxacin has a pyridobenzoxazine ring that appears to decrease the extent of parent compound metabolism. Between 65% and 80% of an administered oral dose of ofloxacin is excreted unchanged via the kidneys within 48 hours of dosing. Studies indicate that less than 5% of an administered dose is recovered in the urine as the desmethyl or N-oxide metabolites. Four to eight percent of an ofloxacin dose is excreted in the feces. This indicates a small degree of biliary excretion of ofloxacin.

The administration of FLOXIN® with food does not affect the C_{max} and AUC_{∞} of the drug, but T_{max} is prolonged.

Clearance of ofloxacin is reduced in patients with impaired renal function (creatinine clearance rate $\leq$50 mL/min), and dosage adjustment is necessary. (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**.)

Following oral administration to healthy elderly subjects (65-81 years of age), maximum plasma concentrations are usually achieved one to two hours after single and multiple twice-daily doses, indicating that the rate of oral absorption is unaffected by age or gender. Mean peak plasma concentrations in elderly subjects were 9-21% higher than those observed in younger subjects. Gender differences in the

pharmacokinetic properties of elderly subjects have been observed. Peak plasma concentrations were 114% and 54% higher in elderly females compared to elderly males following single and multiple twice-daily doses. [This interpretation was based on study results collected from two separate studies.] Plasma concentrations increase dose-dependently with the increase in doses after single oral dose and at steady state. No differences were observed in the volume of distribution values between elderly and younger subjects. As in younger subjects, elimination is mainly by renal excretion as unchanged drug in elderly subjects, although less drug is recovered from renal excretion in elderly subjects. Consistent with younger subjects, less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites in the elderly. A longer plasma half-life of approximately 6.4 to 7.4 hours was observed in elderly subjects, compared with 4 to 5 hours for young subjects. Slower elimination of ofloxacin is observed in elderly subjects as compared with younger subjects which may be attributable to the reduced renal function and renal clearance observed in the elderly subjects. Because ofloxacin is known to be substantially excreted by the kidney, and elderly patients are more likely to have decreased renal function, dosage adjustment is necessary for elderly patients with impaired renal function as recommended for all patients. (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**.)

MICROBIOLOGY

Ofloxacin is a quinolone antimicrobial agent. The mechanism of action of ofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Ofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including ofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to ofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-11}). Although cross-resistance has been observed between ofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to ofloxacin.

Ofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** Section:

Aerobic Gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae (penicillin-susceptible strains)
Streptococcus pyogenes

Aerobic Gram-negative microorganisms

Citrobacter (diversus) koseri
Enterobacter aerogenes
Escherichia coli
Haemophilus influenzae
Klebsiella pneumoniae
Neisseria gonorrhoeae
Proteus mirabilis
Pseudomonas aeruginosa

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ofloxacin.

Other microorganisms

Chlamydia trachomatis

The following *in vitro* data are available, **but their clinical significance is unknown**.

Ofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of ofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-positive microorganisms

Staphylococcus epidermidis (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic Gram-negative microorganisms

Acinetobacter calcoaceticus
Bordetella pertussis
Citrobacter freundii

Enterobacter cloacae
Haemophilus ducreyi
Klebsiella oxytoca
Moraxella catarrhalis
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia marcescens

Anaerobic microorganisms

Clostridium perfringes

Other microorganisms

Chlamydia pneumoniae
Gardnerella vaginalis
Legionella pneumophila
Mycoplasma hominis
Mycoplasma pneumoniae
Ureaplasma urealyticum

Ofloxacin is not active against *Treponema pallidum* (See **WARNINGS**.)

Many strains of other streptococcal species, *Enterococcus* species, and anaerobes are resistant to ofloxacin.

Susceptibility Tests

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae,* methicillin-susceptible *Staphylococcus aureus*, and *Pseudomonas aeruginosa*:

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

For testing *Haemophilus influenzae*:[a]

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* using *Haemophilus* Test Medium[1]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*:[b]

MIC (µg/mL)	Interpretation
≤ 0.25	Susceptible (S)
0.5-1	Intermediate (I)
≥ 2	Resistant (R)

[b] These interpretive standards are applicable only to agar dilution tests using GC agar base and 1% defined growth supplement incubated in 5% CO_2.

For testing *Streptococcus pneumoniae* and *Streptococcus pyogenes*:[c]

MIC (µg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

[c] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ofloxacin powder should provide the following MIC values:

Microorganism		**MIC Range (µg/mL)**
Escherichia coli	ATCC 25922	0.015-0.12
Haemophilus influenzae	ATCC 49247[d]	0.016-0.06
Neisseria gonorrhoeae	ATCC 49226[e]	0.004-0.016
Pseudomonas aeruginosa	ATCC 27853	1-8
Staphylococcus aureus	ATCC 29213	0.12-1
Streptococcus pneumoniae	ATCC 49619[f]	1-4

[d] This quality control range is applicable to only H. influenzae ATCC 49247 tested by a microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[e] This quality control range is applicable only to N. gonorrhoeae ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement incubated in 5% CO_2.

[f] This quality control range is applicable to only S. pneumoniae ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ofloxacin to test the susceptibility of microorganisms to ofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg ofloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae,* methicillin-susceptible *Staphylococcus aureus*, and *Pseudomonas aeruginosa:*

Zone Diameter (mm)	**Interpretation**
≥16	Susceptible (S)
13-15	Intermediate (I)
≤12	Resistant (R)

For testing *Haemophilus influenzae*:[g]

Zone Diameter (mm)	**Interpretation**
≥ 16	Susceptible (S)

[g] This zone diameter standard is applicable only to disk diffusion tests with *Haemophilus influenzae* using *Haemophilus* Test Medium (HTM)[2] incubated in 5% CO_2.

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Neisseria gonorrhoeae*:[h]

Zone Diameter (mm)	Interpretation
≥ 31	Susceptible (S)
25-30	Intermediate (I)
≤ 24	Resistant (R)

[h] These zone diameter standards are applicable only to disk diffusion tests using GC agar base and 1% defined growth supplement incubated in 5% CO_2

For testing *Streptococcus pneumoniae* and *Streptococcus pyogenes*:[i]

Zone Diameter (mm)	Interpretation
≥ 16	Susceptible (S)
13-15	Intermediate (I)
≤ 12	Resistant (R)

[i] These zone diameter standards are applicable only to disk diffusion tests performed using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for ofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg ofloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29-33
Haemophilus influenzae	ATCC 49247[j]	31-40
Neisseria gonorrhoeae	ATCC 49226[k]	43-51
Pseudomonas aeruginosa	ATCC 27853	17-21
Staphylococcus aureus	ATCC 25923	24-28
Streptococcus pneumoniae	ATCC 49619[l]	16-21

[j] This quality control range is applicable only to *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using *Haemophilus* Test Medium (HTM)[2] incubated in 5% CO_2.

[k] This quality control range is applicable only to *N. gonorrhoeae* ATCC 49226 tested by a disk diffusion procedure using GC agar base with 1% defined growth supplement incubated in 5% CO_2.

[l] This quality control range is applicable only to *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLOXIN® (ofloxacin tablets) Tablets and other antibacterial drugs, FLOXIN® (ofloxacin tablets) Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or

modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

FLOXIN® (ofloxacin tablets) Tablets are indicated for the treatment of adults with mild to moderate infections (unless otherwise indicated) caused by susceptible strains of the designated microorganisms in the infections listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute bacterial exacerbations of chronic bronchitis due to *Haemophilus influenzae* or *Streptococcus pneumoniae*.

Community-acquired Pneumonia due to *Haemophilus influenzae* or *Streptococcus pneumoniae*.

Uncomplicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pyogenes,* or *Proteus mirabilis.*

Acute, uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae*. (See **WARNINGS**.)

Nongonococcal urethritis and cervicitis due to *Chlamydia trachomatis.* (See **WARNINGS**.)

Mixed Infections of the urethra and cervix due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae.* (See **WARNINGS**.)

Acute pelvic inflammatory disease (including severe infection) due to *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae*. (See **WARNINGS**.)

NOTE: If anaerobic microorganisms are suspected of contributing to the infection, appropriate therapy for anaerobic pathogens should be administered.

Uncomplicated cystitis due to *Citrobacter diversus, Enterobacter aerogenes, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa.*

Complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Citrobacter diversus**, or *Pseudomonas aeruginosa**.

Prostatitis due to *Escherichia coli.*

* = Although treatment of infections due to this organism in this organ system demonstrated a clinically significant outcome, efficacy was studied in fewer than 10 patients.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to ofloxacin. Therapy with ofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with ofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information not only on the therapeutic effect of the antimicrobial agent but also on the possible emergence of bacterial resistance.

CONTRAINDICATIONS

FLOXIN® (ofloxacin tablets) Tablets is contraindicated in persons with a history of hypersensitivity associated with the use of ofloxacin or any member of the quinolone group of antimicrobial agents.

WARNINGS

Tendinopathy and Tendon Rupture: Fluoroquinolones, including FLOXIN, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. FLOXIN should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

THE SAFETY AND EFFICACY OF OFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers Subsections.)

In the immature rat, the oral administration of ofloxacin at 5 to 16 times the recommended maximum human dose based on mg/kg or 1-3 times based on mg/m^2 increased the incidence and severity of osteochondrosis. The lesions did not regress after 13 weeks of drug withdrawal. Other quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure, and toxic psychosis have been reported in patients receiving quinolones, including ofloxacin. Quinolones, including ofloxacin, may also cause central nervous system stimulation which may lead to: tremors, restlessness/agitation, nervousness/anxiety, lightheadedness, confusion, hallucinations, paranoia and depression, nightmares, insomnia, and rarely suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ofloxacin, the drug should be discontinued and appropriate measures instituted. Insomnia may be more common with ofloxacin than some other products in the quinolone class. As with all quinolones, ofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS.**)

Hypersensitivity Reactions:

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including ofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. This drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS.**)

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including ofloxacin. These events may be severe and generally occur

following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted (See **PRECAUTIONS**: **Information for Patients** and **ADVERSE REACTIONS**).

Peripheral neuropathy:

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ofloxacin. Ofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including FLOXIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management,

protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated. (See **ADVERSE REACTIONS**.)

Ofloxacin has not been shown to be effective in the treatment of syphilis.

Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ofloxacin for gonorrhea should have a follow-up serologic test for syphilis after three months and, if positive, treatment with an appropriate antimicrobial should be instituted.

PRECAUTIONS

General:

Prescribing FLOXIN® (ofloxacin tablets) Tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Adequate hydration of patients receiving ofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer ofloxacin with caution in the presence of renal or hepatic insufficiency/impairment. In patients with known or suspected renal or hepatic insufficiency/impairment, careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of ofloxacin may be reduced. In patients with impaired renal function (creatinine clearance $\leq$50 mg/mL), alteration of the dosage regimen is necessary. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs (See **ADVERSE REACTIONS/Post-Marketing Adverse Events).**

As with other quinolones, ofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk

factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **WARNINGS** and **Drug Interactions**.)

A possible interaction between oral hypoglycemic drugs (e.g., glyburide/glibenclamide) or with insulin and fluoroquinolone antimicrobial agents have been reported resulting in a potentiation of the hypoglycemic action of these drugs. The mechanism for this interaction is not known. If a hypoglycemic reaction occurs in a patient being treated with ofloxacin, discontinue ofloxacin immediately and consult a physician. (See **Drug Interactions** and **ADVERSE REACTIONS**.)

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Torsades de pointes:

Some quinolones, including ofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving quinolones, including ofloxacin. Ofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents.

Information for Patients:

Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue FLOXIN treatment. The risk of severe tendon disorders with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants;
- that antibacterial drugs including FLOXIN® (ofloxacin tablets) Tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When FLOXIN® (ofloxacin tablets) Tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by FLOXIN® (ofloxacin tablets) Tablets or other antibacterial drugs in the future.

- that peripheral neuropathies have been associated with ofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians;
- to drink fluids liberally;
- that mineral supplements, vitamins with iron or minerals, calcium- , aluminum- or magnesium-based antacids, sucralfate or Videx® (didanosine) should not be taken within the two-hour period before or within the two-hour period after taking ofloxacin (See **Drug Interactions**);
- that ofloxacin can be taken without regard to meals;
- that ofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to ofloxacin before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination (See **WARNINGS** and **ADVERSE REACTIONS**);
- that ofloxacin may be associated with hypersensitivity reactions, even following the first dose, to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face; tightness of the throat, hoarseness), or any other symptom of an allergic reaction (See **WARNINGS** and **ADVERSE REACTIONS**);
- that photosensitivity/phototoxicity has been reported in patients receiving quinolone antibiotics. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician;
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic drug, to discontinue ofloxacin immediately if a hypoglycemic reaction occurs and consult a physician (See **PRECAUTIONS: General** and **Drug Interactions**);
- that convulsions have been reported in patients taking quinolones, including ofloxacin, and to notify their physician before taking this drug if there is a history of this condition;
- that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible;
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents. Patients should notify their physicians

if they have any symptoms of prolongation of the QTc interval including prolonged heart palpitations or a loss of consciousness.

Drug Interactions:

Antacids, Sucralfate, Metal Cations, Multivitamins:

Quinolones form chelates with alkaline earth and transition metal cations. Administration of quinolones with antacids containing calcium, magnesium, or aluminum, with sucralfate, with divalent or trivalent cations such as iron, or with multivitamins containing zinc or with Videx® (didanosine) may substantially interfere with the absorption of quinolones resulting in systemic levels considerably lower than desired. These agents should not be taken within the two-hour period before or within the two-hour period after ofloxacin administration. (See **DOSAGE AND ADMINISTRATION**.)

Caffeine:

Interactions between ofloxacin and caffeine have not been detected.

Cimetidine:

Cimetidine has demonstrated interference with the elimination of some quinolones. This interference has resulted in significant increases in half-life and AUC of some quinolones. The potential for interaction between ofloxacin and cimetidine has not been studied.

Cyclosporine:

Elevated serum levels of cyclosporine have been reported with concomitant use of cyclosporine with some other quinolones. The potential for interaction between ofloxacin and cyclosporine has not been studied.

Drugs metabolized by Cytochrome P450 enzymes:

Most quinolone antimicrobial drugs inhibit cytochrome P450 enzyme activity. This may result in a prolonged half-life for some drugs that are also metabolized by this system (e.g., cyclosporine, theophylline/methylxanthines, warfarin) when co-administered with quinolones. The extent of this inhibition varies among different quinolones. (See other **Drug Interactions**.)

Non-steroidal anti-inflammatory drugs:

The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including ofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See **WARNINGS** and **PRECAUTIONS: General**.)

Probenecid:
The concomitant use of probenecid with certain other quinolones has been reported to affect renal tubular secretion. The effect of probenecid on the elimination of ofloxacin has not been studied.

Theophylline:
Steady-state theophylline levels may increase when ofloxacin and theophylline are administered concurrently. As with other quinolones, concomitant administration of ofloxacin may prolong the half-life of theophylline, elevate serum theophylline levels, and increase the risk of theophylline-related adverse reactions. Theophylline levels should be closely monitored and theophylline dosage adjustments made, if appropriate, when ofloxacin is co-administered. Adverse reactions (including seizures) may occur with or without an elevation in the serum theophylline level. (See **WARNINGS** and **PRECAUTIONS: General**.)

Warfarin:
Some quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. Therefore, if a quinolone antimicrobial is administered concomitantly with warfarin or its derivatives, the prothrombin time or other suitable coagulation test should be closely monitored.

Antidiabetic agents (e.g., insulin, glyburide/glibenclamide):
Since disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concurrently with quinolones and an antidiabetic agent, careful monitoring of blood glucose is recommended when these agents are used concomitantly. (See **PRECAUTIONS: General** and **Information for Patients**.)

Interaction with Laboratory or Diagnostic Testing:
Some quinolones, including ofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term studies to determine the carcinogenic potential of ofloxacin have not been conducted.

Ofloxacin was not mutagenic in the Ames bacterial test, *in vitro* and *in vivo* cytogenetic assay, sister chromatid exchange (Chinese Hamster and Human Cell Lines), unscheduled DNA Repair (UDS) using human fibroblasts, dominant lethal assays, or mouse micronucleus assay. Ofloxacin was positive in the UDS test using rat hepatocytes and Mouse Lymphoma Assay.

Pregnancy:

Teratogenic Effects. Pregnancy Category C.

Ofloxacin has not been shown to have any teratogenic effects at oral doses as high as 810 mg/kg/day (11 times the recommended maximum human dose based on mg/m^2 or 50 times based on mg/kg) and 160 mg/kg/day (4 times the recommended maximum human dose based on mg/m^2 or 10 times based on mg/kg) when administered to pregnant rats and rabbits, respectively. Additional studies in rats with oral doses up to 360 mg/kg/day (5 times the recommended maximum human dose based on mg/m^2 or 23 times based on mg/kg) demonstrated no adverse effect on late fetal development, labor, delivery, lactation, neonatal viability, or growth of the newborn. Doses equivalent to 50 and 10 times the recommended maximum human dose of ofloxacin (based on mg/kg) were fetotoxic (i.e., decreased fetal body weight and increased fetal mortality) in rats and rabbits, respectively. Minor skeletal variations were reported in rats receiving doses of 810 mg/kg/day, which is more than 10 times higher than the recommended maximum human dose based on mg/m^2.

There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers:

In lactating females, a single oral 200-mg dose of ofloxacin resulted in concentrations of ofloxacin in milk that were similar to those found in plasma. Because of the potential for serious adverse reactions from ofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Pediatric Use:

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Ofloxacin causes arthropathy (arthrosis) and osteochondrosis in juvenile animals of several species. (See **WARNINGS**.)

Geriatric Use:

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as FLOXIN. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involves the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing FLOXIN to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised

to discontinue FLOXIN and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (See **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS/Post-Marketing Adverse Event Reports**).

In phase 2/3 clinical trials with ofloxacin, 688 patients (14.2%) were ≥ 65 years of age. Of these, 436 patients (9.0%) were between the ages of 65 and 74 and 252 patients (5.2%) were 75 years or older. There was no apparent difference in the frequency or severity of adverse reactions in elderly adults compared with younger adults. The pharmacokinetic properties of ofloxacin in elderly subjects are similar to those in younger subjects. Drug absorption appears to be unaffected by age. Dosage adjustment is necessary for elderly patients with impaired renal function (creatinine clearance rate ≤ 50 mL/min) due to reduced clearance of ofloxacin. In comparative studies, the frequency and severity of most drug-related nervous system events in patients ≥65 years of age were comparable for ofloxacin and control drugs. The only differences identified were an increase in reports of insomnia (3.9% vs 1.5%) and headache (4.7% vs 1.8%) with ofloxacin. It is important to note that these geriatric safety data are extracted from 44 comparative studies where the adverse reaction information from 20 different controls (other antibiotics or placebo) were pooled for comparison with ofloxacin. The clinical significance of such a comparison is not clear. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

Elderly patients may be more sensitive to drug-associated effects on the QT interval. Therefore, precaution should be taken when using ofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. Class IA or Class III antiarrhythmics) or in patients with risk factors for Torsade de pointes (e.g. known QT prolongation, uncorrected hypokalemia). (See **PRECAUTIONS: General**: **Torsades de pointes)**

ADVERSE REACTIONS

The following is a compilation of the data for ofloxacin based on clinical experience with both the oral and intravenous formulations. The incidence of drug-related adverse reactions in patients during Phase 2 and 3 clinical trials was 11%. Among patients receiving multiple-dose therapy, 4% discontinued ofloxacin due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving multiple doses of ofloxacin:

nausea 3%, insomnia 3%, headache 1%, dizziness 1%, diarrhea 1%, vomiting 1%, rash 1%, pruritus 1%, external genital pruritus in women 1%, vaginitis 1%, dysgeusia 1%.

In clinical trials, the most frequently reported adverse events, regardless of relationship to drug, were:

nausea 10%, headache 9%, insomnia 7%, external genital pruritus in women 6%, dizziness 5%, vaginitis 5%, diarrhea 4%, vomiting 4%.

In clinical trials, the following events, regardless of relationship to drug, occurred in 1 to 3% of patients:

Abdominal pain and cramps, chest pain, decreased appetite, dry mouth, dysgeusia, fatigue, flatulence, gastrointestinal distress, nervousness, pharyngitis, pruritus, fever, rash, sleep disorders, somnolence, trunk pain, vaginal discharge, visual disturbances, and constipation.

Additional events, occurring in clinical trials at a rate of less than 1%, regardless of relationship to drug, were:

Body as a whole:	asthenia, chills, malaise, extremity pain, pain, epistaxis
Cardiovascular System:	cardiac arrest, edema, hypertension, hypotension, palpitations, vasodilation
Gastrointestinal System:	Dyspepsia
Genital/Reproductive System:	burning, irritation, pain and rash of the female genitalia; dysmenorrhea; menorrhagia; metrorrhagia
Musculoskeletal System:	arthralgia, myalgia
Nervous System:	seizures, anxiety, cognitive change, depression, dream abnormality, euphoria, hallucinations, paresthesia, syncope, vertigo, tremor, confusion
Nutritional/Metabolic:	thirst, weight loss
Respiratory System:	respiratory arrest, cough, rhinorrhea
Skin/Hypersensitivity:	angioedema, diaphoresis, urticaria, vasculitis
Special Senses:	decreased hearing acuity, tinnitus, photophobia
Urinary System:	dysuria, urinary frequency, urinary retention

The following laboratory abnormalities appeared in ≥1.0% of patients receiving multiple doses of ofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying conditions being treated.

Hematopoietic:	anemia, leukopenia, leukocytosis, neutropenia, neutrophilia, increased band forms, lymphocytopenia, eosinophilia, lymphocytosis, thrombocytopenia, thrombocytosis, elevated ESR
Hepatic:	elevated: alkaline phosphatase, AST (SGOT), ALT (SGPT)
Serum chemistry:	hyperglycemia, hypoglycemia, elevated creatinine, elevated BUN
Urinary:	glucosuria, proteinuria, alkalinuria, hyposthenuria, hematuria, pyuria

Post-Marketing Adverse Events:

Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ofloxacin:

Clinical:

Cardiovascular System:	cerebral thrombosis, pulmonary edema, tachycardia, hypotension/shock, syncope, torsades de pointes
Endocrine/Metabolic:	hyper- or hypoglycemia, especially in diabetic patients on insulin or oral hypoglycemic agents (See **PRECAUTIONS: General** and **Drug Interactions**.)
Gastrointestinal System:	hepatic dysfunction including: hepatic necrosis, jaundice (cholestatic or hepatocellular), hepatitis; intestinal perforation; hepatic failure (including fatal cases); pseudomembranous colitis (the onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), GI hemorrhage; hiccough, painful oral mucosa, pyrosis (See **WARNINGS**.)
Genital/Reproductive System:	vaginal candidiasis
Hematopoietic:	anemia, including hemolytic and aplastic; hemorrhage, pancytopenia, agranulocytosis, leukopenia, reversible bone marrow depression, thrombocytopenia, thrombotic thrombocytopenic purpura, petechiae, ecchymosis/bruising (See **WARNINGS**.)
Musculoskeletal:	tendinitis/rupture; weakness; rhabdomyolysis(See **WARNINGS**.)
Nervous System:	nightmares; suicidal thoughts or acts, disorientation, psychotic reactions, paranoia; phobia, agitation, restlessness, aggressiveness/hostility, manic reaction, emotional lability; peripheral neuropathy, ataxia, incoordination; possible exacerbation of: myasthenia gravis and extrapyramidal disorders; dysphasia, lightheadedness (See **WARNINGS** and **PRECAUTIONS**.)
Respiratory System:	dyspnea, bronchospasm, allergic pneumonitis, stridor (See **WARNINGS**.)
Skin/Hypersensitivity:	anaphylactic (-toid) reactions/shock; purpura, serum sickness, erythema multiforme/Stevens-Johnson Syndrome, erythema nodosum, exfoliative dermatitis, hyperpigmentation, toxic epidermal necrolysis, conjunctivitis, photosensitivity/phototoxicity reaction, vesiculobullous eruption (See **WARNINGS** and **PRECAUTIONS**.)
Special Senses:	diplopia, nystagmus, blurred vision, disturbances of: taste, smell, hearing and equilibrium, usually reversible following discontinuation
Urinary System:	anuria, polyuria, renal calculi, renal failure, interstitial nephritis, hematuria (See **WARNINGS** and **PRECAUTIONS**.)

Laboratory:

Hematopoietic:	prolongation of prothrombin time
Serum chemistry:	acidosis, elevation of: serum triglycerides, serum cholesterol, serum potassium, liver function tests including: GGTP, LDH, bilirubin
Urinary:	albuminuria, candiduria

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

CRYSTALLURIA and CYLINDRURIA HAVE BEEN REPORTED with other quinolones.

OVERDOSAGE

Information on overdosage with ofloxacin is limited. One incident of accidental overdosage has been reported. In this case, an adult female received 3 grams of ofloxacin intravenously over 45 minutes. A blood sample obtained 15 minutes after the completion of the infusion revealed an ofloxacin level of 39.3 μg/mL. In 7 h, the level had fallen to 16.2 μg/mL, and by 24 h to 2.7 μg/mL. During the infusion, the patient developed drowsiness, nausea, dizziness, hot and cold flushes, subjective facial swelling and numbness, slurring of speech, and mild to moderate disorientation. All complaints except the dizziness subsided within 1 h after discontinuation of the infusion. The dizziness, most bothersome while standing, resolved in approximately 9 h. Laboratory testing reportedly revealed no clinically significant changes in routine parameters in this patient.

In the event of an acute overdose, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Ofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

The usual dose of FLOXIN® (ofloxacin tablets) Tablets is 200 mg to 400 mg orally every 12 h as described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., creatinine clearance >50 mL/min). For patients with altered renal function (i.e., creatinine clearance ≤50 mL/min), see the **Patients with Impaired Renal Function** Subsection.

Infection†	**Unit Dose**	**Frequency**	**Duration**	**Daily Dose**
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	q12h	10 days	800 mg
Comm. Acquired Pneumonia	400 mg	q12h	10 days	800 mg
Uncomplicated Skin and Skin Structure Infections	400 mg	q12h	10 days	800 mg
Acute, Uncomplicated Urethral and Cervical Gonorrhea	400 mg	single dose	1 day	400 mg
Nongonococcal Cervicitis/Urethritis due to *C. trachomatis*	300 mg	q12h	7 days	600 mg
Mixed Infection of the urethra and cervix due to *C. trachomatis* and *N. gonorrhoeae*	300 mg	q12h	7 days	600 mg
Acute Pelvic Inflammatory Disease	400 mg	q12h	10-14 days	800 mg
Uncomplicated Cystitis due to *E. coli* or *K. pneumoniae*	200 mg	q12h	3 days	400 mg
Uncomplicated Cystitis due to other approved pathogens	200 mg	q12h	7 days	400 mg
Complicated UTI's	200 mg	q12h	10 days	400 mg
Prostatitis due to *E.Coli*	300 mg	q12h	6 weeks	600 mg

†DUE TO THE DESIGNATED PATHOGENS (See **INDICATIONS AND USAGE**.)

Antacids containing calcium, magnesium, or aluminum; sucralfate; divalent or trivalent cations such as iron; or multivitamins containing zinc; or Videx® (didanosine) should not be taken within the two-hour period before or within the two-hour period after taking ofloxacin. (See **PRECAUTIONS**.)

Patients with Impaired Renal Function:

Dosage should be adjusted for patients with a creatinine clearance ≤50 mL/min. **After a normal initial dose**, dosage should be adjusted as follows:

Creatinine Clearance	Maintenance Dose	Frequency
20-50 mL/min	the usual recommended unit dose	q24h
<20 mL/min	1/2 the usual recommended unit dose	q24h

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady-state of renal function.

Patients with Cirrhosis:

The excretion of ofloxacin may be reduced in patients with severe liver function disorders (e.g., cirrhosis with or without ascites). A maximum dose of 400 mg of ofloxacin per day should therefore not be exceeded.

HOW SUPPLIED

FLOXIN® (ofloxacin tablets) Tablets are supplied as 200 mg light yellow, 300 mg white, and 400 mg pale gold oval, straight-edged, coated tablets. Each tablet is distinguished by an imprint of "FLOXIN" and the appropriate strength. FLOXIN Tablets are packaged in bottles in the following configurations:

200 mg tablets - bottles of 50 (NDC 0062 - 1540-02)
300 mg tablets - bottles of 50 (NDC 0062 - 1541-02)
400 mg tablets - bottles of 100 (NDC 0062 - 1542-01)

FLOXIN Tablets should be stored in well-closed containers. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Keep out of the reach of children.

ANIMAL PHARMACOLOGY

Ofloxacin, as well as other drugs of the quinolone class, has been shown to cause arthropathies (arthrosis) in immature dogs and rats. In addition, these drugs are associated with an increased incidence of osteochondrosis in rats as compared to the incidence observed in vehicle-treated rats. (See **WARNINGS**.) There is no evidence of arthropathies in fully mature dogs at intravenous doses up to 3 times the recommended maximum human dose (on a mg/m^2 basis or 5 times based on mg/kg basis), for a one-week exposure period.

Long-term, high-dose systemic use of other quinolones in experimental animals has caused lenticular opacities; however, this finding was not observed in any animal studies with ofloxacin.

Reduced serum globulin and protein levels were observed in animals treated with other quinolones. In one ofloxacin study, minor decreases in serum globulin and protein levels were noted in female cynomolgus monkeys dosed orally with 40 mg/kg ofloxacin daily for one year. These changes, however, were considered to be within normal limits for monkeys.

Crystalluria and ocular toxicity were not observed in any animals treated with ofloxacin.

FLOXIN® is a trademark of ORTHO-McNEIL PHARMACEUTICAL, INC.

U.S. Patent No. 4,382,892

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January, 1997.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January 1997.

MEDICATION GUIDE
FLOXIN® [Flox in]
(ofloxacin)

Read the Medication Guide that comes with FLOXIN before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about FLOXIN?
FLOXIN belongs to a class of antibiotics called fluoroquinolones. FLOXIN can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take FLOXIN.

Tendon rupture or swelling of the tendon (tendinitis)

- Tendons are tough cords of tissue that connect muscles to bones.
- Pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites can happen in people of all ages who take fluoroquinolone antibiotics, including FLOXIN. The risk of getting tendon problems is higher if you:
  - are over 60 years of age or
  - are taking steroids (corticosteroids) or
  - have had a kidney, heart or lung transplant.
- Swelling of the tendon (tendinitis) and tendon rupture (breakage) have also happened in patients who take fluoroquinolones who do not have the above risk factors.
- Other reasons for tendon ruptures can include:
  - physical activity or exercise
  - kidney failure
  - tendon problems in the past, such as in people with rheumatoid arthritis (RA).
- Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking FLOXIN until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the risk of tendon rupture with continued use of FLOXIN. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
- Tendon rupture can happen while you are taking or after you have finished taking FLOXIN. Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
- Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:
  - hear or feel a snap or pop in a tendon area
  - bruising right after an injury in a tendon area
  - unable to move the affected area or bear weight

- See the section "**What are the possible side effects of FLOXIN?**" for more information about side effects.

What is FLOXIN?
FLOXIN is a fluoroquinolone antibiotic medicine used in adults to treat certain infections caused by certain germs called bacteria. It is not known if FLOXIN is safe and works in people under 18 years of age. Children less than 18 years of age have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking FLOXIN.

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics including FLOXIN do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking FLOXIN.

Who should not take FLOXIN?
Do not take FLOXIN if you have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in FLOXIN. Ask your healthcare provider if you are not sure. See the list of ingredients in FLOXIN at the end of this Medication Guide.

What should I tell my healthcare provider before taking FLOXIN?
See "**What is the most important information I should know about FLOXIN?**"

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have central nervous system problems (such as epilepsy)
- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation."
- have low blood potassium (hypokalemia)
- have a history of seizures
- have kidney problems. You may need a lower dose of FLOXIN if your kidney does not work well.
- have liver problems
- have rheumatoid arthritis (RA) or other history of joint problems
- are pregnant or planning to become pregnant. It is not known if FLOXIN will harm your unborn child
- are breast-feeding or planning to breast-feed. FLOXIN passes into breast milk. You and your healthcare provider should decide whether you will take FLOXIN or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, herbal and dietary supplements. FLOXIN and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take FLOXIN or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See "**What are the possible side effects of FLOXIN?**"
- theophylline
- a blood thinner (warfarin, Coumadin, Jantoven)
- an oral anti-diabetes medicine or insulin
- a medicine to control your heart rate or rhythm (antiarrhythmics) See "**What are the possible side effects of FLOXIN?**"
- an anti-psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See "**What is the most important information I should know about FLOXIN?**".
- Certain medicines may keep FLOXIN from working correctly. Take FLOXIN either 2 hours before or 2 hours after taking these products:
    - an antacid, multivitamin, or other product that has calcium magnesium, aluminum, iron, or zinc.
    - sucralfate (Carafate)
    - didanosine (Videx®, Videx® EC)

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take FLOXIN?

- Take FLOXIN exactly as prescribed by your healthcare provider.
- Take FLOXIN at about the same time each day.
- Drink plenty of fluids while taking FLOXIN.
- FLOXIN can be taken with or without food.
- Do not skip any doses, or stop taking FLOXIN, even if you begin to feel better, until you finish your prescribed treatment, unless:
    - you have tendon effects (see "**What is the most important information I should know about FLOXIN?**"),
    - you have a serious allergic reaction (see "**What are the possible side effects of FLOXIN?**"), or
    - your healthcare provider tells you to stop.
- This will help make sure that all of the bacteria are killed and lower the chance that the bacteria will become resistant to FLOXIN. If this happens, FLOXIN and other antibiotic medicines may not work in the future.
- If you miss a dose of FLOXIN, take it as soon as you remember. Do not take two doses of FLOXIN at the same time. Do not take more than two doses in one day.

- If you take too much, call your healthcare provider or get medical help immediately.

What should I avoid while taking FLOXIN?

- FLOXIN can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how FLOXIN affects you.
- Avoid sunlamps, tanning beds, and try to limit your time in the sun. FLOXIN can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking FLOXIN, call your healthcare provider right away. You should use sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of FLOXIN?

FLOXIN can cause side effects that may be serious or even cause death. See "**What is the most important information I should know about FLOXIN?**"

Other serious side effects of FLOXIN include:

- **Central Nervous System Effects:** Seizures have been reported in people who take fluoroquinolone antibiotics including FLOXIN. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking FLOXIN will change your risk of having a seizure.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of FLOXIN. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:
  - feel lightheaded
  - seizures
  - hear voices, see things, or sense things that are not there (hallucinations)
  - feel restless
  - tremors
  - feel anxious or nervous
  - confusion
  - depression
  - trouble sleeping
  - nightmares
  - feel more suspicious (paranoia)
  - suicidal thoughts or acts
- **Serious allergic reactions**: Allergic reactions can happen in people taking fluoroquinolones, including FLOXIN, even after only one dose. Stop taking FLOXIN and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:
  - hives
  - trouble breathing or swallowing
  - swelling of the lips, tongue, face
  - throat tightness, hoarseness

  - rapid heartbeat
  - faint
  - yellowing of the skin or eyes. Stop taking FLOXIN and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to FLOXIN (a liver problem).
- **Skin rash:** Skin rash may happen in people taking FLOXIN, even after only one dose. Stop taking FLOXIN at the first sign of a skin rash and call your healthcare provider. Skin rash may be sign of a more serious reaction to FLOXIN.
- **Intestine infection** (Pseudomembranous colitis): Pseudomembranous colitis can happen with most antibiotics, including FLOXIN. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may also have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.
- **Changes in sensation and possible nerve damage** (Peripheral Neuropathy): Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including FLOXIN. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:
  - pain
  - burning
  - tingling
  - numbness
  - weakness
- **Serious heart rhythm changes** (QT prolongation and torsades de pointes): Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. FLOXIN may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:
  - who are elderly
  - with a family history of prolonged QT interval
  - with low blood potassium (hypokalemia)
  - who take certain medicines to control heart rhythm (antiarrhythmics)

  FLOXIN may need to be stopped to prevent permanent nerve damage
- **Sensitivity to sunlight** (photosensitivity): See "**What should I avoid while taking FLOXIN?**"
- **Low blood sugar** (hypoglycemia). People taking FLOXIN and other fluoroquinolone medicines with oral anti-diabetes medicines or with insulin can get low blood sugar (hypoglycemia). Follow your healthcare provider's instructions for how often to check your blood sugar. If you have diabetes and you get low blood sugar while taking FLOXIN, stop taking FLOXIN right away and call your healthcare provider right away. Your antibiotic medicine may need to be changed.

The most common side effects of FLOXIN include:

- Sleep problems
- headache
- dizziness
- nausea
- vomiting
- diarrhea
- itching
- external genital itching in women
- vaginal inflammation (vaginitis)
- taste changes

FLOXIN may cause false-positive urine screening results for opiates when testing is done with some commercially available kits. A positive result should be confirmed using a more specific test.

These are not all the possible side effects of FLOXIN. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1- 800-FDA-1088.

How should I store FLOXIN?

- Store FLOXIN at 59° to 86° F(15°F to 30°C).
- Keep the bottle that FLOXIN comes in closed tightly.
- **Keep FLOXIN and all medicines out of the reach of children.**

General information about FLOXIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FLOXIN for a condition for which it is not prescribed. Do not give FLOXIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about FLOXIN. If you would like more information about FLOXIN, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about FLOXIN that is written for healthcare professionals. For more information call 1-800-526-7736 or go to www.FLOXIN.com.

What are the ingredients in FLOXIN?

- Active ingredient: ofloxacin
- Inactive ingredients: anhydrous lactose, modified corn starch, hydroxypropyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and may also contain synthetic yellow iron oxide.

Revised September 2008

Ortho-McNeil, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc

Raritan, NJ USA 08869

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Exhibit G

Search results from the "OB_Rx" table for query on "020634."

Active Ingredient:	LEVOFLOXACIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	LEVAQUIN
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	250MG
Application Number:	020634
Product Number:	001
Approval Date:	Dec 20, 1996
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	LEVOFLOXACIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	LEVAQUIN
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	500MG
Application Number:	020634
Product Number:	002
Approval Date:	Dec 20, 1996
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	LEVOFLOXACIN
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	LEVAQUIN
Applicant:	ORTHO MCNEIL JANSSEN
Strength:	750MG
Application Number:	020634
Product Number:	003
Approval Date:	Sep 8, 2000
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through September, 2008

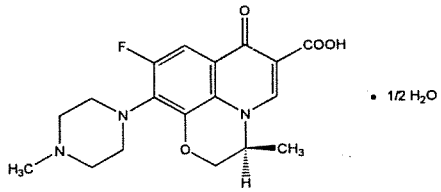
Patent and Generic Drug Product Data Last Updated: October 20, 2008

LEVAQUIN® (levofloxacin) TABLETS
LEVAQUIN® (levofloxacin) ORAL SOLUTION
LEVAQUIN® (levofloxacin) INJECTION
LEVAQUIN® (levofloxacin in 5% dextrose) INJECTION

To reduce the development of drug-resistant bacteria and maintain the effectiveness of LEVAQUIN® (levofloxacin) and other antibacterial drugs, LEVAQUIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

LEVAQUIN® (levofloxacin) is a synthetic broad spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

The chemical structure is: 

Its empirical formula is $C_{18}H_{20}FN_3O_4 \bullet \frac{1}{2} H_2O$ and its molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered *soluble to freely soluble* in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL) and is considered *freely soluble* in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9.

Levofloxacin has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: $Al^{+3} > Cu^{+2} > Zn^{+2} > Mg^{+2} > Ca^{+2}$.

LEVAQUIN Tablets are available as film-coated tablets and contain the following inactive ingredients:

250 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.

500 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron oxides.

750 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80.

LEVAQUIN Oral Solution, 25 mg/mL is a multi-use self-preserving aqueous solution of levofloxacin with pH ranging from 5.0 – 6.0. The appearance of LEVAQUIN Oral Solution may range from clear yellow to clear greenish-yellow. This does not adversely affect product potency.

LEVAQUIN Oral Solution contains the following inactive ingredients: sucrose, glycerin, sucralose, hydrochloric acid, purified water, propylene glycol, artificial and natural flavors, benzyl alcohol, ascorbic acid, and caramel color. It may also contain a solution of sodium hydroxide for pH adjustment.

LEVAQUIN Injection in Single-Use Vials is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. LEVAQUIN Injection in Premix Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. The appearance of LEVAQUIN Injection may range from a clear yellow to a greenish-yellow solution. This does not adversely affect product potency.

LEVAQUIN Injection in Single-Use Vials contains levofloxacin in Water for Injection. LEVAQUIN Injection in Premix Flexible Containers is a dilute, non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in 5% Dextrose (D_5W). Solutions of hydrochloric acid and sodium hydroxide may have been added to adjust the pH.

The flexible container is fabricated from a specially formulated non-plasticized, thermoplastic copolyester (CR3). The amount of water that can permeate from the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic containers.

CLINICAL PHARMACOLOGY

The mean ±SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral (p.o.) tablet, oral solution, or intravenous (i.v.) doses of levofloxacin are summarized in Table 1.

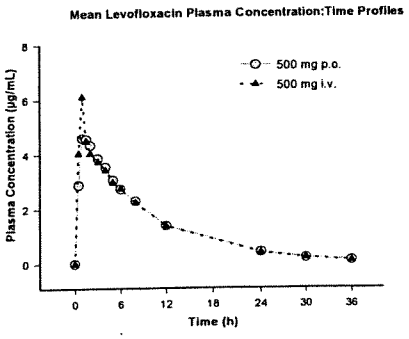
Absorption

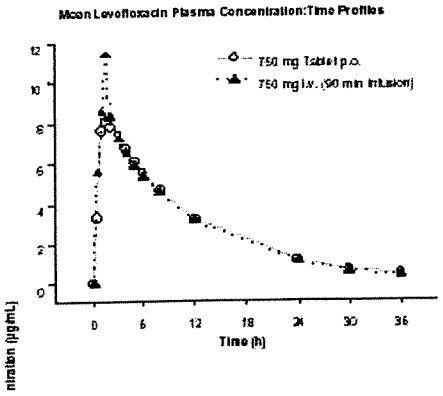
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean ±SD peak plasma concentration attained was 6.2 ±1.0 µg/mL after a 500 mg dose infused over 60 minutes and 11.5 ±4.0 µg/mL after a 750 mg dose infused over 90 minutes. Levofloxacin oral solution and tablet formulations are bioequivalent.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ±1.4 and 0.5 ±0.2 µg/mL after the 500 mg doses, and 8.6 ±1.9 and 1.1 ±0.4 µg/mL after the 750 mg doses, respectively. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily i.v. regimens were approximately 6.4 ±0.8 and 0.6 ±0.2 µg/mL after the 500 mg doses, and 12.1 ±4.1 and 1.3 ±0.71 µg/mL after the 750 mg doses, respectively.

Oral administration of 500mg LEVAQUIN with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, levofloxacin tablets can be administered without regard to food. It is recommended that levofloxacin oral solution be taken 1 hour before, or 2 hours after eating.

The plasma concentration profile of levofloxacin after i.v. administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and i.v. routes of administration can be considered interchangeable. (See following chart.)





Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg levofloxacin, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5- fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 µg/g over a 24-hour period after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 µg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method.

Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

Special Populations

Geriatric:

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy elderly subjects (66 - 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary.

Pediatric:

The pharmacokinetics of levofloxacin in pediatric subjects have not been studied.

Gender:

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race:

The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 non-white. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal insufficiency:

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD. (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION**.)

Hepatic insufficiency:

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Bacterial infection:

The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

Drug-drug interactions:

The potential for pharmacokinetic drug interactions between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate, and antacids has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)

Table 1. Mean ±SD Levofloxacin PK Parameters

Regimen	C_{max} (μg/mL)	T_{max} (h)	AUC (μg•h/mL)	CL/F[1] (mL/min)	Vd/F[2] (L)	$t_{1/2}$ (h)	CL_R (mL/min)
Single dose							
250 mg p.o.tablet[3]	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21
500 mg p.o. tablet[3]*	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg oral solution[12]	5.8 ± 1.8	0.8 ± 0.7	47.8 ± 10.8	183 ± 40	112 ± 37.2	7.0 ± 1.4	ND
500 mg i.v.[3]	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg p.o.tablet[5*]	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	ND
750 mg i.v.[5]	11.5 ±4.0[4]	ND	110 ±40	126 ±39	75 ± 13	7.5 ± 1.6	ND
Multiple dose							
500 mg q24h p.o. tablet[3]	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg q24h i.v.[3]	6.4 ± 0.8	ND	54.6 ± 11.1	158 ± 29	91 ± 12	7.0 ± 0.8	99 ± 28
500 mg or 250 mg q24h i.v., patients with bacterial infection[6]	8.7± 4.0[7]	ND	72.5 ± 51.2[7]	154 ± 72	111 ± 58	ND	ND
750 mg q24h p.o. tablet[5]	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg q24h i.v.[5]	12.1 ± 4.1[4]	ND	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	ND
500 mg p.o. tablet single dose, effects of gender and age:							
Male[8]	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
Female[9]	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
Young[10]	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6.0 ± 0.9	140 ± 33
Elderly[11]	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2.0	91 ± 29
500 mg p.o. single dose tablet, patients with renal insufficiency:							
CL_{CR} 50-80 mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	88 ± 10	ND	9.1 ± 0.9	57 ± 8
CL_{CR} 20-49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
CL_{CR} <20 mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	ND

[1] clearance/bioavailability
[2] volume of distribution/bioavailability
[3] healthy males 18-53 years of age
[4] 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose
[5] healthy male and female subjects 18-54 years of age
[6] 500 mg q48h for patients with moderate renal impairment (CL_{CR} 20-50 mL/min) and infections of the respiratory tract or skin
[7] dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling
[8] healthy males 22-75 years of age
[9] healthy females 18-80 years of age
[10] young healthy male and female subjects 18-36 years of age
[11] healthy elderly male and female subjects 66-80 years of age
[12] healthy males and females 19-55 years of age.

*Absolute bioavailability; F = 0.99 ± 0.08 from a 500-mg tablet and F = 0.99 ± 0.06 from a 750-mg tablet;
ND = not determined.

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible)

Staphylococcus aureus (methicillin-susceptible strains)

Staphylococcus epidermidis (methicillin-susceptible strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]*)

Streptococcus pyogenes

* MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2µg/ml), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Aerobic gram-negative microorganisms

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms

Chlamydia pneumoniae

Mycoplasma pneumoniae

Levofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of plasma levels as a surrogate marker in a rhesus monkey model for anthrax (post-exposure). (See **INDICATIONS AND USAGE** and **ADDITIONAL INFORMATION - INHALATIONAL ANTHRAX**).

The following *in vitro* data are available, **but their clinical significance is unknown.**

Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus

Streptococcus (Group C/F)

Streptococcus (Group G)

Streptococcus agalactiae

Streptococcus milleri

Viridans group *streptococci*

Aerobic gram-negative microorganisms

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter (diversus) koseri

Citrobacter freundii

Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea (Enterobacter) agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Anaerobic gram-positive microorganisms

Clostridium perfringens

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae, Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, and *Pseudomonas aeruginosa:*

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[a]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[b] and *S. pyogenes*:

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal,

and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard levofloxacin powder should give the following MIC values:

Microorganism		MIC (µg/mL)
Enterococcus faecalis	ATCC 29212	0.25 – 2
Escherichia coli	ATCC 25922	0.008 - 0.06
Escherichia coli	ATCC 35218	0.015 - 0.06
Haemophilus influenzae	ATCC 49247[c]	0.008 - 0.03
Pseudomonas aeruginosa	ATCC 27853	0.5 – 4
Staphylococcus aureus	ATCC 29213	0.06 - 0.5
Streptococcus pneumoniae	ATCC 49619[d]	0.5 – 2

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg levofloxacin disk should be interpreted according to the following criteria:

For testing *Enterobacteriaceae*, *Enterococcus faecalis*, methicillin-susceptible *Staphylococcus* species, and *Pseudomonas aeruginosa*:

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

For *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[e]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)

[e] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus pneumoniae*[f] and *S. pyogenes*:

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

[f] These zone diameter standards for *Streptococcus* spp. including *S. pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg levofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29 - 37
Haemophilus influenzae	ATCC 49247g	32 - 40
Pseudomonas aeruginosa	ATCC 27853	19 - 26
Staphylococcus aureus	ATCC 25923	25 - 30
Streptococcus pneumoniae	ATCC 49619h	20 - 25

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM).[2]

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of LEVAQUIN® (levofloxacin) and other antibacterial drugs, LEVAQUIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

LEVAQUIN Tablets/Injection and Oral Solution are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below. LEVAQUIN Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis.*

Acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis.*

Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended. (See **CLINICAL STUDIES**.)

Community-acquired pneumonia due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant strains [MDRSP])*, *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES.**)

* MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2µg/ml), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes,* or *Proteus mirabilis*.

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes*.

Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or methicillin-susceptible *Staphylococcus epidermidis*.

Complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa.*

Acute pyelonephritis (mild to moderate) caused by *Escherichia coli.*

Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus*.

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.* (See **DOSAGE AND ADMINISTRATION** and **ADDITIONAL INFORMATION - INHALATIONAL ANTHRAX**).

Levofloxacin has not been tested in human for the post-exposure prevention of inhalation anthrax. However, plasma concentrations achieved in humans are reasonably likely to predict efficacy. (See **ADDITIONAL INFORMATION - INHALATIONAL ANTHRAX**).

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin. Therapy with levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Levofloxacin is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product.

WARNINGS

THE SAFETY AND EFFICACY OF LEVOFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use**, **Pregnancy**, and **Nursing Mothers** subsections.)

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species. The relevance of these findings to the clinical use of levofloxacin is unknown. (See **ANIMAL PHARMACOLOGY**.)

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS

disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) (See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS.)**

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS**.)

Peripheral Neuropathy: Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling,

numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS**.)

Tendon Effects: Ruptures of the shoulder, hand, Achilles tendon, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

PRECAUTIONS

General

Prescribing LEVAQUIN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Because a rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 OR 90 MINUTES DEPENDING ON THE DOSAGE. (See **DOSAGE AND ADMINISTRATION**.)

Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Administer levofloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION.**)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **WARNINGS** and **Drug Interactions**.)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately. (See **Drug Interactions** and **ADVERSE REACTIONS**.)

Torsades de pointes: Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving quinolones, including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Information for Patients

Patients should be advised:

- Patients should be counseled that antibacterial drugs including LEVAQUIN® (levofloxacin) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When LEVAQUIN is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by LEVAQUIN or other antibacterial drugs in the future;
- that peripheral neuropathies have been associated with levofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians;
- to drink fluids liberally;
- that antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx® (didanosine) should be taken at least two hours before or two hours after oral levofloxacin administration. (See **Drug Interactions**);
- that levofloxacin oral tablets can be taken without regard to meals;
- that levofloxacin oral solution should be taken 1 hour before or 2 hours after eating;
- that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. (See **WARNINGS** and **ADVERSE REACTIONS**);
- to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;
- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema

(e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction. (See **WARNINGS** and **ADVERSE REACTIONS**);

- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs;
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a physician. (See **PRECAUTIONS: General** and **Drug Interactions**);
- that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin;
- that convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions

Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN Tablets:

While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of LEVAQUIN Tablets with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or Videx® (didanosine) may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.

LEVAQUIN Injection:

There are no data concerning an interaction of **intravenous** quinolones with **oral** antacids, sucralfate, multivitamins, Videx® (didanosine), or metal cations. However, no quinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line. (See **DOSAGE AND ADMINISTRATION**.)

Theophylline:

No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels. (See **WARNINGS** and **PRECAUTIONS: General**.)

Warfarin:

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

Cyclosporine:

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{½}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin:

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving

healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine:

No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $t_{½}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and CL_R were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

Non-steroidal anti-inflammatory drugs:

The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See **WARNINGS** and **PRECAUTIONS: General**.)

Antidiabetic agents:

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Interactions with Laboratory or Diagnostic Testing:

Some quinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 μg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 μg/g at C_{max}.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S. typhimurium* and *E. coli)*, CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

Pregnancy: Teratogenic Effects. Pregnancy Category C.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause

arthropathy and osteochondrosis in juvenile animals of several species. (See **WARNINGS**.)

Geriatric Use

In phase 3 clinical trials, 1,190 levofloxacin-treated patients (25%) were ≥65 years of age. Of these, 675 patients (14%) were between the ages of 65 and 74 and 515 patients (11%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using levofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsades de pointes (e.g. known QT prolongation, uncorrected hypokalemia). (See **PRECAUTIONS: GENERAL**: Torsades de Pointes).

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The incidence of drug-related adverse reactions in patients during Phase 3 clinical trials conducted in North America was 6.7%. Among patients receiving levofloxacin therapy, 4.1% discontinued levofloxacin therapy due to adverse experiences.

In all Phase III trials, the overall incidence, type and distribution of adverse events was similar in patients receiving levofloxacin doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:

nausea 1.5%, diarrhea 1.2%, vaginitis 0.5%, insomnia 0.4%, abdominal pain 0.4%, flatulence 0.2%, pruritus 0.2%, dizziness 0.3%, rash 0.3%, dyspepsia 0.3%, genital moniliasis 0.1%, moniliasis 0.2%, taste perversion 0.2%, vomiting 0.3%, injection site pain 0.2%, injection site reaction 0.1%, injection site inflammation 0.1%, constipation 0.1%, fungal infection 0.1%, genital pruritis

0.1%, headache 0.2%, nervousness 0.1%, rash erythematous 0.1%, urticaria 0.1%, anorexia 0.1%, somnolence 0.1%, agitation 0.1%, rash maculo-papular (<0.1%), dry mouth 0.2%, tremor 0.1%, condition aggravated 0.1%, allergic reaction 0.1%.

In clinical trials, the following events occurred in >3% of patients, regardless of drug relationship:

nausea 6.8%, headache 5.8%, diarrhea 5.4%, insomnia 4.6%, constipation 3.1%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:

abdominal pain 2.5%, dizziness 2.4%, vomiting 2.4%, dyspepsia 2.3%, vaginitis 1.3%, rash 1.4%, chest pain 1.2%, pruritus 1.2%, sinusitis 1.1%, dyspnea 1.3%, fatigue 1.2%, flatulence 1.2%, pain 1.3%, back pain 1.2%, rhinitis 1.2%, pharyngitis 1.1%.

In clinical trials, the following events, of potential medical importance, occurred at a rate of 0.1% to 0.9%, regardless of drug relationship:

Body as a Whole – General Disorders:	Ascites, allergic reaction, asthenia, , edema, fever, headache, hot flashes, influenza-like symptoms, leg pain, malaise, rigors, substernal chest pain, syncope, multiple organ failure,changed temperature sensation, withdrawal syndrome
Cardiovascular Disorders, General:	Cardiac failure, hypertension, hypertension aggravated, hypotension, postural hypotension
Central and Peripheral Nervous System Disorders:	Convulsions (seizures), hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contractions, migraine, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo, encephalopathy, abnormal gait, leg cramps, intracranial hypertension, ataxia
Gastro-Intestinal System Disorders:	Dry mouth, dysphagia, esophagitis, gastritis, gastroesophageal reflux, G.I. hemorrhage, glossitis, intestinal obstruction, pancreatitis, tongue edema, melena, stomatitis
Hearing and Vestibular Disorders:	Earache, ear disorder NOS, tinnitus
Heart Rate and Rhythm Disorders:	Arrhythmia, arrhythmia ventricular, atrial fibrillation, bradycardia, cardiac arrest, ventricular fibrillation, heart block, palpitation, supraventricular tachycardia, ventricular tachycardia, tachycardia
Liver and Biliary System Disorders:	Abnormal hepatic function, cholecystitis, cholelithiasis, hepatic enzymes increased, hepatic failure, jaundice
Metabolic and Nutritional Disorders:	Hypomagnesemia, thirst, dehydration, electrolyte abnormality, fluid overload, gout, hyperglycemia, hyperkalemia, hypernatremia, hypoglycemia, hypokalemia, hyponatremia,

	hypophosphatemia, nonprotein nitrogen increase, weight decrease
Musculo-Skeletal System Disorders:	Arthralgia, arthritis, arthrosis, myalgia, osteomyelitis, skeletal pain, synovitis, tendonitis, tendon disorder
Myo, Endo, Pericardial and Valve Disorders:	Angina pectoris, myocardial infarction
Neoplasms:	Carcinoma, thrombocythemia
Other Special Senses Disorders:	Parosmia, taste perversion
Platelet, Bleeding and Clotting Disorders:	Hematoma, epistaxis, prothrombin decreased, pulmonary embolism, purpura, thrombocytopenia
Psychiatric Disorders:	Abnormal dreaming, agitation, anorexia, anxiety, confusion, depression, hallucination, impotence, nervousness, paroniria, sleep disorder, somnolence
Red Blood Cell Disorders:	Anemia
Reproductive Disorders:	Dysmenorrhea, leucorrhea
Resistance Mechanism Disorders:	Abscess, bacterial infection, fungal infection, herpes simplex, moniliasis, otitis media, sepsis, infection
Respiratory System Disorders:	Airways obstruction, aspiration, asthma, bronchitis, bronchospasm, chronic obstructive airway disease, coughing, hemoptysis, epistaxis, hypoxia, laryngitis, pleural effusion, pleurisy, pneumonitis, pneumonia, pneumothorax, pulmonary edema, respiratory depression, respiratory disorder, respiratory insufficiency, upper respiratory tract infection
Skin and Appendages Disorders:	Alopecia, bullous eruption, dry skin, eczema, genital pruritus, increased sweating, rash, skin disorder, skin exfoliation, skin ulceration, urticaria
Urinary System Disorders:	Abnormal renal function, acute renal failure, hematuria, oliguria, urinary incontinence, urinary retention, urinary tract infection
Vascular (Extracardiac) Disorders:	Flushing, cerebrovascular disorder, gangrene, phlebitis, purpura, thrombophlebitis (deep)
Vision Disorders:	Abnormal vision, eye pain, conjunctivitis
White Cell and RES Disorders:	Agranulocytosis, granulocytopenia, leukocytosis, lymphadenopathy, WBC abnormal NOS

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.

Crystalluria and cylindruria have been reported with other quinolones.

The following markedly abnormal laboratory values appeared in >2% of patients receiving levofloxacin. It is not known whether this abnormality was caused by the drug or the underlying condition being treated.

Hematology: decreased lymphocytes (2.2%)

Post-Marketing Adverse Reactions

Additional adverse events reported from worldwide post-marketing experience with levofloxacin include: allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, increased International Normalized Ratio (INR)/prothrombin time, peripheral neuropathy, rhabdomyolysis, Stevens-Johnson Syndrome, tendon rupture, torsades de pointes, vasodilation.

OVERDOSAGE

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg i.v. produced significant mortality in rodents. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

LEVAQUIN Injection should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED. Levofloxacin Injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. (See PRECAUTIONS.)

Single-use vials require dilution prior to administration. (See PREPARATION FOR ADMINISTRATION.)

The usual dose of LEVAQUIN Tablets or Oral Solution (25 mg/mL) is 250 mg or 500 mg or 750 mg administered orally every 24 hours, as indicated by infection and described in the following dosing chart. The usual dose of LEVAQUIN Injection is 250 mg or 500 mg administered by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as indicated

by infection and described in the following dosing chart. Levofloxacin tablets can be administered without regard to food. It is recommended that levofloxacin oral solution be taken 1 hour before or 2 hours after eating. These recommendations apply to patients with normal renal function (i.e., creatinine clearance > 80 mL/min). For patients with altered renal function see the **Patients with Impaired Renal Function** subsection. Oral doses should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx® (didanosine), chewable/buffered tablets or the pediatric powder for oral solution.

Patients with Normal Renal Function

Infection[1]	Unit Dose	Freq.	Duration[2]	Daily Dose
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Comm. Acquired Pneumonia	750 mg[3]	q24h	5 days	750 mg
Nosocomial Pneumonia	750 mg	q24h	7-14 days	750 mg
Acute Bacterial Sinusitis	500 mg	q24h	10-14 days	500 mg
Acute Bacterial Sinusitis	750 mg	q24h	5 days	750 mg
Complicated SSSI	750 mg	q24h	7-14 days	750 mg
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Uncomplicated SSSI	500 mg	q24h	7-10 days	500 mg
Chronic Bacterial Prostatitis	500 mg	q24h	28 days	500 mg
Complicated UTI	250 mg	q24h	10 days	250 mg
Acute pyelonephritis	250 mg	q24h	10 days	250 mg
Uncomplicated UTI	250 mg	q24h	3 days	250 mg
Inhalational anthrax (post-exposure) Adult[4,5]	500 mg	q24h	60 days[5]	500mg

[1] **DUE TO THE DESIGNATED PATHOGENS** (See **INDICATIONS AND USAGE**.)

[2] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

[3] Efficacy of this alternative regimen has been demonstrated to be effective for infections caused by *Streptococcus pneumoniae* (excluding MDRSP), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

[4] Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit (See **CLINICAL PHARMACOLOGY** and **ADDITIONAL INFORMATION - INHALATIONAL ANTHRAX**).

[5] The safety of levofloxacin in adults for durations of therapy beyond 28 days has not been studied. Prolonged levofloxacin therapy in adults should only be used when the benefit outweighs the risk (See **ADDITIONAL INFORMATION – INHALATIONAL ANTHRAX).**

Patients with Impaired Renal Function

Renal Status	Initial Dose	Subsequent Dose

Renal Status	Initial Dose	Subsequent Dose
Acute Bacterial Exacerbation of Chronic Bronchitis/Comm. Acquired Pneumonia/Acute Bacterial Sinusitis/Uncomplicated SSSI/Chronic Bacterial Prostatitis/Inhalational Anthrax (post-exposure)		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	500 mg	250 mg q24h
CL_{CR} from 10 to 19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
Complicated SSSI/Nosocomial Pneumonia/ Comm. Acquired Pneumonia/Acute Bacterial Sinusitis		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	750 mg	750 mg q48h
CL_{CR} from 10 to 19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h
Complicated UTI/Acute Pyelonephritis		
$CL_{CR} \geq 20$ mL/min	No dosage adjustment required	
CL_{CR} from 10 to 19 mL/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

CL_{CR}=creatinine clearances
CAPD=chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance:

Mean: Creatinine Clearance (mL/min) =

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

Preparation of Levofloxacin Injection for Administration

LEVAQUIN Injection in Single-Use Vials:

LEVAQUIN Injection is supplied in single-use vials containing a concentrated levofloxacin solution with the equivalent of 500 mg (20 mL vial) and 750 mg (30 mL vial) of levofloxacin in Water for Injection, USP. The 20 mL and 30 mL vials each contain 25 mg of levofloxacin/mL. **THESE LEVAQUIN INJECTION SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION.** (See COMPATIBLE INTRAVENOUS SOLUTIONS.) The concentration of the resulting diluted solution should be 5 mg/mL prior to administration.

This intravenous drug product should be inspected visually for particulate matter prior to administration. Samples containing visible particles should be discarded.

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. **Since the vials are for single-use only, any unused portion remaining in the vial should be discarded. When used to prepare two 250 mg doses from the 20 mL vial containing 500 mg of levofloxacin, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be prepared and stored for subsequent use.** (See **Stability of LEVAQUIN Injection Following Dilution**.)

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Prepare the desired dosage of levofloxacin according to the following chart:

Desired Dosage Strength	From Appropriate Vial, Withdraw Volume	Volume of Diluent	Infusion Time
250 mg	10 mL (20 mL Vial)	40 mL	60 min
500 mg	20 mL (20 mL Vial)	80 mL	60 min
750 mg	30 mL (30 mL Vial)	120 mL	90 min

For example, to prepare a 500 mg dose using the 20 mL vial (25 mg/mL), withdraw 20 mL and dilute with a compatible intravenous solution to a total volume of 100 mL.

Compatible Intravenous Solutions: Any of the following intravenous solutions may be used to prepare a 5 mg/mL levofloxacin solution with the approximate pH values:

Intravenous Fluids	Final pH of LEVAQUIN Solution
0.9% Sodium Chloride Injection, USP	4.71
5% Dextrose Injection, USP	4.58
5% Dextrose/0.9% NaCl Injection	4.62
5% Dextrose in Lactated Ringers	4.92
Plasma-Lyte® 56/5% Dextrose Injection	5.03
5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection	4.61
Sodium Lactate Injection (M/6)	5.54

LEVAQUIN Injection Premix in Single-Use Flexible Containers (5 mg/mL):
LEVAQUIN Injection is also supplied in flexible containers containing a premixed, ready-to-use levofloxacin solution in D_5W for single-use. The fill volume is either 50 or 100 mL for the 100 mL flexible container or 150 mL for the 150 mL container. **NO FURTHER DILUTION OF THESE PREPARATIONS ARE NECESSARY. Consequently each 100 mL and 150 mL premix flexible container already contains a dilute solution with the equivalent of 250 mg or 500 mg (100 mL container), and 750 mg of levofloxacin (150 mL container) in 5% Dextrose (D_5W). The concentration of each presentation is 5 mg/mL of levofloxacin solution.**

Since the premix flexible containers are for single-use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in flexible containers or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Instructions for the Use of LEVAQUIN Injection Premix in Flexible Containers

To open:

1. Tear outer wrap at the notch and remove solution container.
2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.
3. Do not use if the solution is cloudy or a precipitate is present.
4. Use sterile equipment.
5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. **NOTE: See full directions on administration set carton.**
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of LEVAQUIN Injection in Premix Flexible Containers.
6. Open flow control clamp to expel air from set. Close clamp.
7. Regulate rate of administration with flow control clamp.

Stability of LEVAQUIN Injection as Supplied

When stored under recommended conditions, LEVAQUIN Injection, as supplied in 20 mL and 30 mL vials, or 100 mL and 150 mL flexible containers, is stable through the expiration date printed on the label.

Stability of LEVAQUIN Injection Following Dilution

LEVAQUIN Injection, when diluted in a compatible intravenous fluid to a concentration of 5 mg/mL, is stable for 72 hours when stored at or below 25°C (77°F) and for 14 days when stored under refrigeration at 5°C (41°F) in plastic intravenous containers. Solutions that are diluted in a compatible intravenous solution and frozen in glass bottles or plastic intravenous containers are stable for 6 months when stored at -20°C (-4°F). **THAW FROZEN SOLUTIONS AT ROOM TEMPERATURE 25°C (77°F) OR IN A REFRIGERATOR 8°C (46°F). DO NOT FORCE THAW BY MICROWAVE IRRADIATION OR WATER BATH IMMERSION. DO NOT REFREEZE AFTER INITIAL THAWING.**

HOW SUPPLIED

LEVAQUIN Tablets

LEVAQUIN (levofloxacin) Tablets are supplied as 250, 500, and 750 mg capsule-shaped, coated tablets. LEVAQUIN Tablets are packaged in bottles and in unit-dose blister strips in the following configurations:

250 mg tablets are terra cotta pink and are imprinted: "LEVAQUIN" on one side and "250" on the other side.

bottles of 50 (NDC 0045-1520-50)

unit-dose/100 tablets (NDC 0045-1520-10)

500 mg tablets are peach and are imprinted: "LEVAQUIN" on one side and "500" on the other side

bottles of 50 (NDC 0045-1525-50)

unit-dose/100 tablets (NDC 0045-1525-10)

750 mg tablets are white and are imprinted "LEVAQUIN" on one side and "750" on the other side

bottles of 20 (NDC 0045-1530-20)

unit-dose/100 tablets (NDC 0045-1530-10)

LEVA-pak 5 tablets (NDC 0045-1530-05)

LEVAQUIN Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed containers.

LEVAQUIN Tablets are manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

LEVAQUIN Oral Solution

LEVAQUIN Oral Solution is supplied in a 16 oz. multi-use bottle (NDC 0045-1515-01). Each bottle contains 480 mL of the 25 mg/mL levofloxacin oral solution.

LEVAQUIN Oral Solution should be stored at 25°C (77°F); excursions permitted to 15° - 30°C (59° to 86°F) [refer to USP controlled room temperature].

LEVAQUIN Oral Solution is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Ortho Pharmaceutical in Manati, Puerto Rico, 00674.

LEVAQUIN Injection

Single-Use Vials:

LEVAQUIN (levofloxacin) Injection is supplied in single-use vials. Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 mL vials and 750 mg of levofloxacin in 30 mL vials.

25 mg/mL, 20 mL vials (NDC 0045-0069-51)
25 mg/mL, 30 mL vials (NDC 0045-0065-55)

LEVAQUIN Injection in Single-Use Vials should be stored at controlled room temperature and protected from light.

LEVAQUIN Injection in Single-Use Vials is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Janssen Pharmaceutica N.V., Beerse, Belgium. Premix in Flexible Containers:

LEVAQUIN (levofloxacin in 5% dextrose) Injection is supplied as a single-use, premixed solution in flexible containers. Each bag contains a dilute solution with the equivalent of 250, 500, or 750 mg of levofloxacin, respectively, in 5% Dextrose (D_5W).

5 mg/mL (250 mg), 100 mL flexible container, 50 mL fill (NDC 0045-0067-01)
5 mg/mL (500 mg), 100 mL flexible container, 100 mL fill (NDC 0045-0068-01)
5 mg/mL (750 mg), 150 mL flexible container, 150 mL fill (NDC 0045-0066-01)

LEVAQUIN Injection Premix in Flexible Containers should be stored at or below 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat and protect from freezing and light.

LEVAQUIN Injection Premix in Flexible Containers is manufactured for OMP DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by Hospira, Inc., Lake Forest, IL 60045.

CLINICAL STUDIES

Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous levofloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7-15 days to intravenous imipenem/cilastatin (500-1000 mg q6-8 hours daily) followed by oral ciprofloxacin (750 mg q12 hours daily) for a total of 7-15 days. Levofloxacin-treated patients received an average of 7 days of intravenous

therapy (range: 1-16 days); comparator-treated patients received an average of 8 days of intravenous therapy (range: 1-19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the levofloxacin arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the levofloxacin arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented *Pseudomonas aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (N=11) or piperacillin/tazobactam (N=4) in the levofloxacin arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the levofloxacin arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S. aureus* infection.

Clinical success rates in clinically and microbiologically evaluable patients at the posttherapy visit (primary study endpoint assessed on day 3-15 after completing therapy) were 58.1% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the posttherapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen were as follows:

Pathogen	N	Levofloxacin No. (%) of PatientsMicrobiologic /ClinicalOutcomes	N	Imipenem/Cilastatin No. (%) of Patients Microbiologic / Clinical Outcomes
MSSA[a]	21	14 (66.7) / 13 (61.9)	19	13 (68.4) / 15 (78.9)
P. aeruginosa[b]	17	10 (58.8) / 11 (64.7)	17	5 (29.4) / 7 (41.2)
S. marcescens	11	9 (81.8) / 7 (63.6)	7	2 (28.6) / 3 (42.9)
E. coli	12	10 (83.3) / 7 (58.3)	11	7 (63.6) / 8 (72.7)
K. pneumoniae[c]	11	9 (81.8) / 5 (45.5)	7	6 (85.7) / 3 (42.9)
H. influenzae	16	13 (81.3) /10 (62.5)	15	14 (93.3) / 11 (73.3)
S. pneumoniae	4	3 (75.0) / 3 (75.0)	7	5 (71.4) / 4 (57.1)

[a] Methicillin-susceptible *S. aureus.*
[b] See above text for use of combination therapy.
[c] The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study.

Community-Acquired Bacterial Pneumonia

7 to 14 Day Treatment Regimen

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in two pivotal clinical studies. In the first study,

590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies were as follows:

Pathogen	No. Pathogens	Microbiologic Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Community-Acquired Bacterial Pneumonia

5-Day Treatment Regimen

To evaluate the safety and efficacy of higher dose and shorter course of levofloxacin, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicenter study comparing levofloxacin 750 mg, i.v. or p.o., q.d. for five days or levofloxacin 500 mg i.v. or p.o., q.d. for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 90.9% in the levofloxacin 750 mg group and 91.1% in the levofloxacin 500 mg group. The 95% CI for the difference of response rates (levofloxacin 750 minus levofloxacin 500) was [-5.9, 5.4]. In the clinically evaluable population (31-38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the levofloxacin

750 mg group and 2 out of 147 patients in the levofloxacin 500 mg group. Given the small numbers observed, the significance of this finding can not be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in the table below.

	Eradication rate
Penicillin susceptible *S. pneumoniae*	19/20
Haemophilus influenzae	12/12
Haemophilus parainfluenzae	10/10
Mycoplasma pneumoniae	26/27
Chlamydia pneumoniae	13/15

Community-Acquired Pneumonia Due to Multi-Drug Resistant *Streptococcus pneumoniae* (MDRSP)*

LEVAQUIN was effective for the treatment of community-acquired pneumonia caused by multi-drug resistant *Streptococcus pneumoniae* (MDRSP)*. Of 40 microbiologically evaluable patients with MDRSP isolates, 38 patients (95.0%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in the table below.

*MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2µg/ml), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Clinical and Bacteriological Success Rates for Levofloxacin-Treated MDRSP* CAP Patients (Population: Valid for Efficacy)

Screening Susceptiblity	Clinical Success		Bacteriological Success**	
	n/N[a]	%	n/N[b]	%
Penicillin-resistant	16/17	94.1	16/17	94.1
2nd generation cephalosporin resistant	31/32	96.9	31/32	96.9
Macrolide-resistant	28/29	96.6	28/29	96.6
Trimethoprim/ Sulfamethoxazole resistant	17/19	89.5	17/19	89.5
Tetracycline-resistant	12/12	100	12/12	100

[a] n = the number of microbiologically evaluable patients who were clinical successes; N = number of microbiologically evaluable patients in the designated resistance group.

[b] n = the number of MDRSP isolates eradicated or presumed eradicated in microbiologically evaluable patients; N = number of MDRSP isolates in a designated resistance group.

* MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC ≥2ug/ml) 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole..

** One patient had a respiratory isolate that was resistant to tetracycline, cefuroxime, macrolides and TMP/SMX and intermediate to penicillin and a blood isolate that was intermediate to penicillin and cefuroxime and resistant to the other classes. The patient is included in the database based on respiratory isolate.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in the table below.

Resistant *Streptococcus pneumoniae* clinical success and bacteriologic eradication rates

S. pn with MDRSP	Clinical Success	Bacteriologic Eradication
Resistant to 2	17/18 (94.4%)	17/18 (94.4%)
Resistant to 3	14/15 (93.3%)	14/15 (93.3%)
Resistant to 4	7/7 (100%)	7/7 (100%)
Resistant to 5	0	0
Bacteremias with MDRSP	8/9 (89%)	8/9 (89%)

Complicated Skin and Skin Structure Infections

Three hundred ninety-nine patients were enrolled in an open-label, randomized, comparative study for complicated skin and skin structure infections. The patients were randomized to receive either levofloxacin 750 mg QD (IV followed by oral), or an approved comparator for a median of 10 ± 4.7 days. As is expected in complicated skin and skin structure infections, surgical procedures were performed in the levofloxacin and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the levofloxacin-treated patients and 44% of the

comparator treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2-5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral levofloxacin 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5-18 days after completion of therapy was 75.0% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented below:

	Levofloxacin (N=136)		Ciprofloxacin (N=125)	
Pathogen	N	Eradication	N	Eradication
E. coli	15	14 (93.3%)	11	9 (81.8%)
E. faecalis	54	39 (72.2%)	44	33 (75.0%)
**S. epidermidis*	11	9 (81.8%)	14	11 (78.6%)

*Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.

Eradication rates for *S. epidermidis* when found with other co-pathogens are consistent with rates seen in pure isolates.

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5-18 days after completion of therapy were 75.0% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical

long-term success (24-45 days after completion of therapy) rates were 66.7% for the levofloxacin-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for levofloxacin minus ciprofloxacin).

Acute Bacterial Sinusitis

Levofloxacin is approved for the treatment of acute bacterial sinusitis (ABS) using either 750 mg PO x 5 days or 500 mg PO QD x 10-14 days. To evaluate the safety and efficacy of a high dose short course of levofloxacin, 780 outpatient adults with clinically and radiologically determined acute bacterial sinusitis were evaluated in a double-blind, randomized, prospective, multicenter study comparing levofloxacin 750 mg p.o. q.d. for five days to levofloxacin 500 mg p.o. q.d. for 10 days.

Clinical success rates (defined as complete or partial resolution of the pre-treatment signs and symptoms of ABS to such an extent that no further antibiotic treatment was deemed necessary) in the microbiologically evaluable population were 91.4% (139/152) in the levofloxacin 750 mg group and 88.6% (132/149) in the levofloxacin 500 mg group at the test of cure visit (95% CI [-4.2, 10.0] for levofloxacin 750 mg minus levofloxacin 500 mg).

Rates of clinical success by pathogen in the microbiologically evaluable population who had specimens obtained by antral tap at study entry showed comparable results for the five- and ten-day regimens at the test-of-cure visit 22 days post treatment.

Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture

Pathogen	*Levofloxacin 750 mg x 5 days*	*Levofloxacin 500 mg x 10 days*
Streptococcus pneumoniae *	25/27 (92.6%)	26/27 (96.3%)
Haemophilus influenzae *	19/21 (90.5%)	25/27 (92.6%)
Moraxella catarrhalis *	10/11 (90.9%)	13/13 (100%)

* Note: Forty percent of the subjects in this trial had specimens obtained by sinus endoscopy. The efficacy data for subjects whose specimen was obtained endoscopically were comparable to those presented in the above table.

ADDITIONAL INFORMATION - INHALATION ANTHRAX

The mean plasma concentrations of levofloxacin associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult patients receiving oral and intravenous regimens. (See **DOSAGE AND ADMINISTRATION**).

Levofloxacin pharmacokinetics were evaluated in various populations. Levofloxacin plasma concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication. The mean (±s.d.) steady-state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.1 ± 0.8 and 6.2 ± 1.0 µg/mL, respectively; and the corresponding total exposure is 47.9 ± 6.8 and 48.3 ± 5.4 µg ·h/mL, respectively.

In adults, the safety of levofloxacin for treatment durations of up to 28 days is well characterized. However, information pertaining to extended use at 500 mg daily up to 60 days is limited.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD_{50} (~2.7 X 10^6) spores (range 17 - 118 LD_{50}) of *B. anthracis* (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 µg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 2.79 to 4.87 µg/mL. Mean steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 µg/mL. Mortality due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) [P = 0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

ANIMAL PHARMACOLOGY

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) In immature dogs (4-5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin for 8 or 9 consecutive days, with an 18-week recovery period, exhibited musculoskeletal clinical signs by the final dose at

dose levels ≥ 2.5 mg/kg (approximately >0.2- fold the potential therapeutic dose (1500 mg q24h) based upon plasma AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (equivalent to and 3-fold greater than the potential therapeutic dose, respectively). All musculoskeletal clinical signs were resolved by week 5 of recovery; synovitis was resolved by the end of the 18-week recovery period; whereas, articular cartilage erosions and chondropathy persisted.

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other quinolones.

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

In vitro and *in vivo* studies in animals indicate that levofloxacin is neither an enzyme inducer or inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically Sixth Edition. Approved Standard NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests Eighth Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

Patient Information About:
LEVAQUIN®
(levofloxacin) Tablets
250 mg Tablets, 500 mg Tablets, and 750 mg Tablets
And
LEVAQUIN® (levofloxacin) Oral Solution, 25 mg/mL

This leaflet contains important information about LEVAQUIN® (levofloxacin), and should be read completely before you begin treatment. This leaflet does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This leaflet does not list all benefits and risks of LEVAQUIN®. The medicine described here can be prescribed only by a licensed health care professional. If you have any questions about LEVAQUIN® talk to your health care professional. Only your health care professional can determine if LEVAQUIN® is right for you.

What is LEVAQUIN®?

LEVAQUIN® is a quinolone antibiotic used to treat lung, sinus, skin, and urinary tract infections caused by certain germs called bacteria. LEVAQUIN® kills many of the types of bacteria that can infect the lungs, sinuses, skin, and urinary tract and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). LEVAQUIN®, like other antibiotics, does not kill viruses.

You should contact your health care professional if you think that your condition is not improving while taking LEVAQUIN®. LEVAQUIN® Tablets are terra cotta pink for the 250 mg tablet, peach colored for the 500 mg tablet, or white for the 750 mg tablet. The appearance of LEVAQUIN Oral Solution may range from clear yellow to clear greenish-yellow.

How and when should I take LEVAQUIN®?

LEVAQUIN® should be taken once a day for 3, 5, 7, 10, 14 or 28 days depending on your prescription. LEVAQUIN® Tablets should be swallowed and may be taken with or without food. LEVAQUIN® Oral Solution should be taken 1 hour before or 2 hours after eating. Try to take the tablet and oral solution at the same time each day and drink fluids liberally.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of LEVAQUIN® even if you missed a dose by mistake. You should not take a double dose.

Who should not take LEVAQUIN®?

You should not take LEVAQUIN® if you have ever had a severe allergic reaction to any of the group of antibiotics known as "quinolones" such as ciprofloxacin. Serious and occasionally fatal allergic reactions have been reported in patients receiving therapy with quinolones, including LEVAQUIN®.

If you are pregnant or are planning to become pregnant while taking LEVAQUIN®, talk to your health care professional before taking this medication. LEVAQUIN® is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

LEVAQUIN® is not recommended for children.

What are possible side effects of LEVAQUIN®?

LEVAQUIN® is generally well tolerated. The most common side effects caused by LEVAQUIN®, which are usually mild, include nausea, diarrhea, itching, abdominal pain, dizziness, flatulence, rash and vaginitis in women.

You should be careful about driving or operating machinery until you are sure LEVAQUIN® is not causing dizziness.

Allergic reactions have been reported in patients receiving quinolones including LEVAQUIN®, even after just one dose. If you develop hives, skin rash or other symptoms of an allergic reaction, you should stop taking this medication and call your health care professional.

Ruptures of shoulder, hand, or Achilles tendons have been reported in patients receiving quinolones, including LEVAQUIN®. If you develop pain, swelling, or rupture of a tendon you should stop taking LEVAQUIN® and contact your health care professional.

Some quinolone antibiotics have been associated with the development of phototoxicity ("sunburns" and "blistering sunburns") following exposure to sunlight or other sources of ultraviolet light such as artificial ultraviolet light used in tanning

salons. LEVAQUIN® has been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking LEVAQUIN®.

If you have diabetes and you develop a hypoglycemic reaction while on LEVAQUIN®, you should stop taking LEVAQUIN® and call your health care professional.

Convulsions have been reported in patients receiving quinolone antibiotics including LEVAQUIN®. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions.

Quinolones, including LEVAQUIN®, may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and rarely, suicidal thoughts or acts.

If you notice any side effects not mentioned in this leaflet or you have concerns about the side effects you are experiencing, please inform your health care professional.

For more complete information regarding levofloxacin, please refer to the full prescribing information, which may be obtained from your health care professional, pharmacist, or the Physicians Desk Reference (PDR).

What about other medicines I am taking?

Taking warfarin (Coumadin®) and LEVAQUIN® together can further predispose you to the development of bleeding problems. If you take warfarin, be sure to tell your health care professional.

Many antacids and multivitamins may interfere with the absorption of LEVAQUIN® and may prevent it from working properly. You should take LEVAQUIN® either 2 hours before or 2 hours after taking these products.

It is important to let your health care professional know all of the medicines you are using.

Other information

Take your dose of LEVAQUIN® once a day.

Complete the course of medication even if you are feeling better.

Keep this medication out of the reach of children.

Some quinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.

[ADD LOGO]
OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey, USA 08869

U.S. Patent No. 5,053,407.
Revised June 2006

[ADD OMP, HOSPIRA and BEERSE CODES, respectively]

Exhibit H

29

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

FEB 27 1997

#29

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs (HFY-20)
Food and Drug Administration
5600 Fishers Lane, Room 15-22
Rockville, MD 20857

Dear Mr. Wilson:

The attached application for patent term extension of U.S. Patent No. 5,053,407 was filed on February 18, 1997, under 35 U.S.C. § 156. U.S. Patent No. 5,053,407 issued on October 1, 1991 from an application that was filed on June 20, 1986. Accordingly, the original expiration date of the patent is October 1, 2008.

The assistance of your Office is requested in confirming that the product identified in the application, LEVAQUIN™, has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period after the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act (FFDCA), this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156 if the approval of LEVAQUIN™ is the first permitted marketing or use of the active ingredient thereof under the provision of law under which regulatory review occurred. Applicant has stated that "the corresponding racemate Floxin" has been previously approved (note page 16, numbered section 13 of the application). Floxin was approved under section 505 of the FFDCA. See 5 U.S.C. § 156(a)(5)(A).

Telephone inquiries regarding this communication should be directed to the undersigned at (703) 306-3159.

Karin Tyson
Legal Advisor
Special Program Law Office
Office of the Deputy Assistant Commissioner
for Patent Policy and Projects

cc: Louis Gubinsky and Joseph J. Ruch, Jr.
Sughrue, Mion, Zinn, MacPeak & Seas
2100 Pennsylvania Ave., NW
Suite 800
Washington, D.C. 20037-3202

30

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

#30

JUL 24 1997

JUL 18 1997

Re: LEVAQUIN™
Docket No. 97E-0109

Stephen G. Kunin
Deputy Assistant Commissioner for
Patent Policy and Projects
Office of the Assistant Commissioner for Patents
U.S. Patent and Trademark Office
Crystal Park Building 2, Suite 919
Washington, D.C. 20231

Dear Mr. Kunin:

This is in regard to the application for patent term extension for U.S. Patent No. 5,053,407 filed by Daiichi Pharmaceutical Co., Ltd. under 35 U.S.C. § 156. The human drug product identified in the patent extension application is LEVAQUIN™ (levofloxacin), which was assigned New Drug Application (NDA) No. 20-634.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). Our records also indicate that it represents the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1), and interpreted by the courts in Glaxo Operations UK Ltd. v. Quigg, 706 F. Supp 1224 (E.D. Va. 1989), aff'd, 894 F. 2d 392 (Fed. Cir. 1990).

The NDA was approved on December 20, 1996, which makes the submission of the patent term extension application on February 18, 1997, timely within the meaning of 35 U.S.C. § 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. § 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the Federal Register, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely,

Ronald L. Wilson, Director
Health Assessment Policy Staff
Office of Health Affairs

cc: Louis Gubinsky and Joseph J. Ruch, Jr.
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